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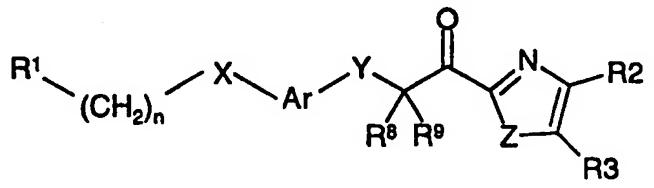


(I)

(57) Abstract

Compounds of formula (I) are disclosed, processes for their preparation, pharmaceutical compositions containing the compounds and the use of the compounds as pharmaceuticals. There are also provided chemical intermediates useful for the preparation of the compounds. The compounds are useful as pharmaceuticals, especially for the treatment of inflammatory disease.

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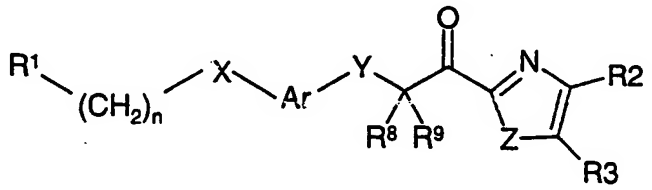
# NOVEL COMPOUNDS

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing the compounds and the use of the compounds as pharmaceuticals. There are also provided chemical intermediates useful for the preparation of the compounds.

According to the invention, there is provided a compound of formula I



I

wherein:-

$R^1$ represents hydrogen, C1 to 12 alkyl, phenyl or a 5 or 6 membered heterocyclic ring containing from 1 to 3 atoms selected from O, N or S, which alkyl, phenyl or heterocyclic ring is optionally substituted by halogen, or which alkyl is optionally substituted by a group J, where J is phenyl or phenyl fused with one or two benzene rings, or biphenylyl, optionally ring substituted by 1 to 3 heteroatoms selected from O, N or S, each group J being optionally substituted by C1 to 6 alkyl, hydroxy, C1 to 6 alkoxy, nitro or halogen;

for $R^2$ and $R^3$:-

(i) $R^2$ represents hydrogen, C1 to 6 alkyl or $R^{10}$-B; and
$R^3$ represents hydrogen, C1 to 6 hydroxyalkyl, C3 to 9 alkenylcarboxyl or $R^{10}$-B, wherein $R^{10}$ represents C1 to 6 alkyl and B represents COOH, $PO_3H_2$, $OPO_3H_2$, $SO_3H$, $OSO_3H$, tetrazolyl, $CONR^{11}OH$ or $CONHSO_2R^{11}$, $R^{11}$ representing hydrogen or C1 to 6 alkyl; or

(ii) $R^2$ and $R^3$ together represent a benzo ring or a six membered aromatic heterocyclic ring containing 1 to 3 nitrogen atoms, which benzo or heterocyclic ring is optionally substituted by $R^4$, wherein $R^4$ represents hydrogen, C1 to 6 alkoxy, C1 to 6 carboxyalkoxy, C3 to 9 alkenylcarboxyl, $R^{10}$-B or $-(CH_2)_pCO_2PG$,
wherein $R^{10}$ represents C1 to 6 alkyl and B represents COOH, $PO_3H_2$, $OPO_3H_2$, $SO_3H$, $OSO_3H$, tetrazolyl, $CONR^{11}OH$ or $CONHSO_2R^{11}$, $R^{11}$ representing

hydrogen or C1 to 6 alkyl, and PG is allyl or *tert*-butyl and p represents zero or an integer from 1 to 6;

$R^8$ and $R^9$ independently represent hydrogen, methyl, C1 to 6 alkyl, aryl or heteroaryl, or together $R^8$ and $R^9$ represent C3 to 6 cycloalkyl or a 3, 4, 5 or 6 membered heterocyclic ring containing from 1 to 3 atoms selected from O, N or S;

Ar represents phenyl, or phenyl fused with one or two benzo rings, or biphenylyl optionally ring substituted with 1 to 3 heteroatoms selected from O, N or S, each Ar group being optionally substituted by C1 to 6 alkyl, hydroxy, C1 to 6 alkoxy, nitro or halogen;

X represents O, S, $SO_2$, $CH_2$ or SO;

Y represents O, $NR^5$ or $(CH_2)_a$, where a represents an integer from 1 to 12 and $R^5$ represents hydrogen or C1 to 6 alkyl;

Z represents O, S, CH=CH, N=N, N=CH or $NR^5$, where $R^5$ represents hydrogen or C1 to 6 alkyl; and

n represents an integer from 1 to 12;

or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

According to the invention, there is also provided a compound of formula I or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, for use as a pharmaceutical.

Another aspect of the invention provides the use of a compound of formula I or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory disease.

The invention further provides a method of treating, or reducing the risk of, inflammatory disease in a patient suffering from, or at risk of, said disease, wherein the method comprises administering to the patient a compound of formula I or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

Suitably $R^1$ represents hydrogen, C1 to 12 alkyl, phenyl or a 5 or 6 membered heterocyclic ring containing from 1 to 3 atoms selected from O, N or S, which alkyl, phenyl or heterocyclic ring is optionally substituted by halogen, or which alkyl is optionally substituted by a group J, where J is phenyl or phenyl fused with one or two benzene rings, or biphenylyl, optionally ring substituted by 1 to 3 heteroatoms selected from O, N or S, each group J being optionally substituted by C1 to 6 alkyl, hydroxy, C1 to 6 alkoxy, nitro or halogen. Examples of suitable 5 or 6-membered heterocyclic rings include thiophene,

furan, pyrrole, pyridyl and pyrimidine rings. Preferably, $R^1$ represents phenyl, dichlorophenyl (eg, 3,5- or 3,4-dichlorophenyl) or methyl. More preferably $R^1$ represents phenyl or dichlorophenyl.

Preferably, $R^2$ represents hydrogen, methyl or $-(CH_2)_4CO_2H$.

Preferably, when $R^3$ is according to option (i), it represents hydrogen, $-(CH_2)_2OH$, $-CO_2H$, $-(CH_2)_3CO_2H$, $-(CH_2)_2CO_2H$ or $CH=CH-CO_2H$.

Preferably, when $R^2$ and $R^3$ are according to option (ii), $R^4$ represents hydrogen, OMe, $-CO_2H$, $-(CH_2)_2CO_2H$, $-OCH_2CO_2H$ or $-(CH_2)_pCO_2PG$, where PG is allyl or *tert*-butyl and p represents zero or an integer from 1 to 6. More preferably when $R^2$ and $R^3$ are according to option (ii), $R^4$ represents hydrogen, OMe, $-CO_2H$, $-(CH_2)_2CO_2H$ or $-OCH_2CO_2H$.

Preferably, a represents an integer from 1 to 3.

Preferably, Y represents O or $CH_2$.

Preferably, X represents O or S or $SO_2$.

Preferably, Z represents O, S, CH=CH, NH or NMe.

Preferably, n represents 1, 5 or 9.

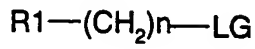
Preferably, $R^8$ represents hydrogen or methyl. More preferably $R^8$ represents hydrogen.

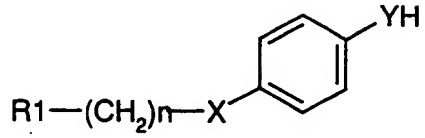
Preferably, $R^9$ represents hydrogen, methyl, phenyl or isopropyl. More preferably $R^9$ represents hydrogen.

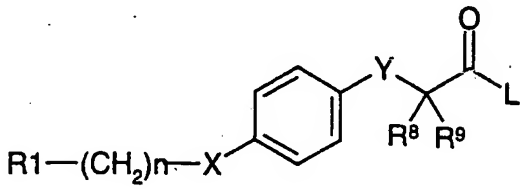
Preferred compounds are those exemplified herein, both in free base form and as pharmaceutically acceptable salts.

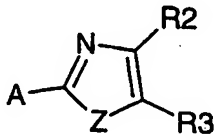
Chemical intermediates of formulae II to XXI are useful for producing compounds of formula I or pharmaceutically acceptable salts, enantiomers or tautomers thereof. Novel

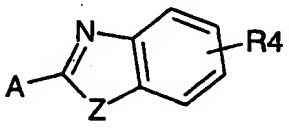
intermediates of formulae II to XXI form a further aspect of the invention. Formulae II to XXI are as follows:-

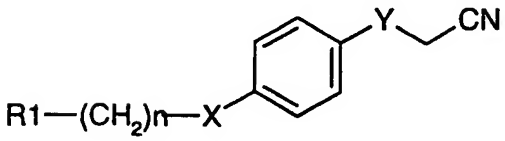
II 

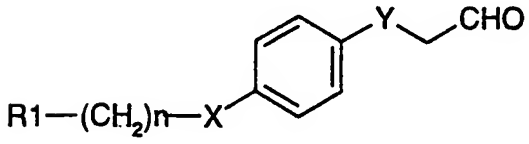
III 

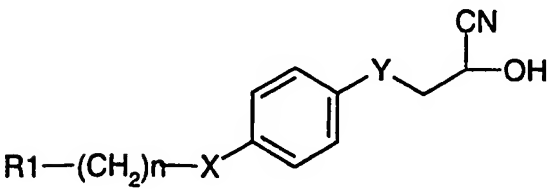
IV 

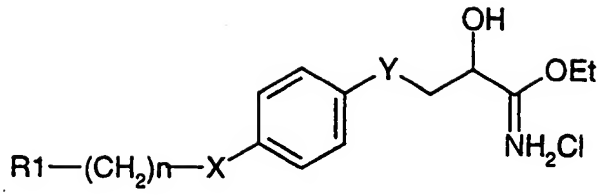
V 

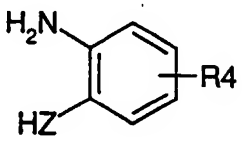
VI 

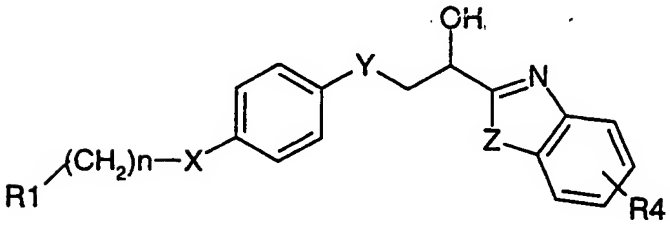
VII 

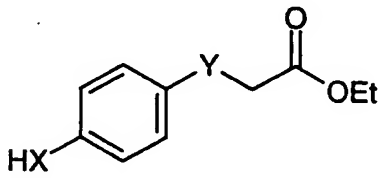
VIII 

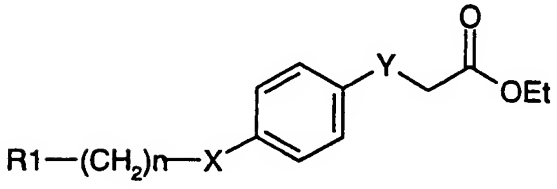
IX 

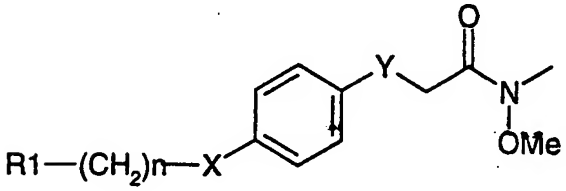
X 

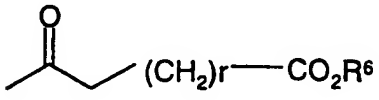
XI 

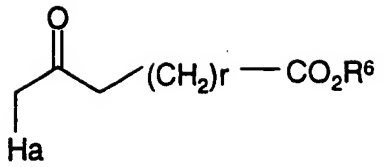
XII 

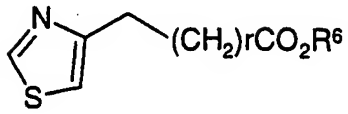
XIII 

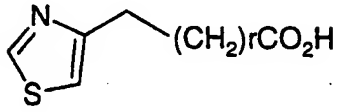
XIV 

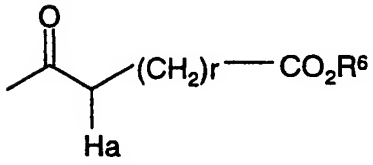
XV 

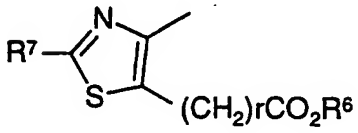
XVI 

XVII 

XVIII 

XIX 

XX 

XXI 

wherein

$R^1$, $R^2$, $R^4$, $R^8$, $R^9$, X, Y and n are as defined above;

Z is as defined above or represents N-C($Ph_3$);

$R^3$ is as defined above, or represents -CH=CH$CO_2R^6$, -CHO or -$(CH_2)_2$OTBDMS, wherein TBDMS is dimethyl(1,1-dimethylethyl)silyl;

$R^6$ represents hydrogen or C1 to 6 alkyl;

$R^7$ represents hydrogen, $NH_2$ or halogen;

L and LG each represents a leaving group;

Ha represents halogen;

A represents hydrogen or halogen; and

r represents zero or an integer from 1 to 6.

In preferred embodiments of formulae II to VI:-

X = O or S or $SO_2$;
Y = O;
Z = S, NMe or N-C($Ph_3$);
$R^1$ = Me, phenyl, 3,5-dichlorophenyl or 3,4-dichlorophenyl;
$R^2$ = H, Me, $(CH_2)CO_2R^6$ or $(CH_2)_4CO_2H$;
$R^3$ = H, $(CH_2)_mCO_2R^6$, $(CH_2)_2OH$, $(CH_2)_2OTBDMS$, $(CH_2)_mCO_2H$, $CH=CHCO_2R^6$ or -CHO;
$R^4$ = H, OMe, $OCH_2CO_2PG$, $OCH_2CO_2H$ or $CO_2H$;
$R^8$ = H or Me;
$R^9$ = Me, Ph or C2-6 alkyl;
n = 1, 5 or 9;
m = 0, 2 or 3;
L = OEt or 1-pyrrolidinyl;
LG = Br, OMesyl or OTosyl;
A = H or Br;
PG=*tert*-Butyl.

In preferred embodiments of formulae VII toXII:-
X = O or S;
Y = O;
Z = O or NH;
$R^1$ = phenyl, 3,5-dichlorophenyl or 3,4-dichlorophenyl;
$R^4$ = H, OMe, $OCH_2CO_2PG$ or $(CH_2)_pCO_2PG$, where p=0 or 2;
n = 1 or 5;
PG = allyl, hydrogen or *tert*-butyl.

In preferred embodiments of formulae XIII to XV:-
X = O;
Y = $CH_2$;
$R^1$ = phenyl;
n = 5.

In preferred embodiments of formulae XVI to XXI:-
r = 0, 2 or 3;
$R^6$ = hydrogen or methyl; and
$R^7$ = hydrogen, Br or $NH_2$.

The process mentioned above, for the preparation of compounds of formula I or their pharmaceutically acceptable salts, enantiomers or tautomers, comprises:-

(a) reacting a compound of formula IV, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, with a compound of formula V, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein formulae IV and V are as defined above; or

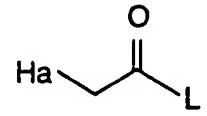
(b) reacting a compound of formula IV, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, with a compound of formula VI, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein formulae IV and VI are as defined above; or
(c) oxidising a compound of formula XII, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein formula XII is as defined above; or
(d) preparing a compound of formula I, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein X represents $SO_2$, by oxidising a compound of formula I, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein X represents S.

In options (a) and (b), the reaction may for example be performed in the presence of BuLi.

In option (c), Dess-Martin oxidation may for example be used.

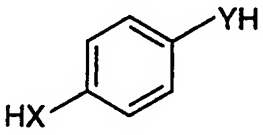
In option (d), oxidation may for example be performed using oxone.

Compounds of formula IV may be prepared by reaction of compounds of formula III with the following compound:-

XXII 


wherein Ha represents halogen (preferably Br) and L is as defined above. The reaction may be performed in the presence of a base.

Compounds of formula III may be prepared by reaction of compounds of formula II with the following compound:-

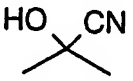
XXIII 


wherein X and Y are as defined above. The reaction may be performed in the presence of a base.

Compounds of formula XII may be prepared by reaction of compounds of formula X with compounds of formula XI.

Compounds of formula X may be prepared by reaction of compounds of formula IX with an acyl halide in an alcohol, eg acetyl chloride in ethanol.

Compounds of formula IX may be prepared by reaction of compounds of formula VIII with the following compound:-

XXIV 

This reaction is performed in the presence of TEA (triethylamine).

Compounds of formula VIII may be prepared by reaction of compounds of formula VII, XIV or XV with Dibal-H (diisobutylaluminium hydride).

Compounds of formula VII may be prepared by reaction of compounds of formula III with the following compound:-

XXV 

wherein Ha represents halogen, preferably Br. This reaction may be performed in the presence of a base.

Compounds of formula XV may be prepared from compounds of formula XIV. The conditions for this reaction are firstly, hydrolysis of the ester to the acid. Then conversion of the acid to acid chloride. Then reaction of the acid chloride with N-methoxy-N-methylamine to give XV.

Compounds of formula XIV may be prepared by reacting compounds of formula XIII with compounds of formula II. This reaction may be performed in the presence of base.

The thiazole intermediates of formula XIX may be prepared by reacting compounds of formula XVIII with LiOH in a suitable solvent, eg THF-$H_2O$.

Compounds of formula XVIII may be prepared by reacting compounds of formula XVII with formamide in the presence of $P_2S_5$.

Compounds of formula XVII may be prepared by reacting compounds of formula XVI with $Ha_2$ (where Ha represents halogen, preferably Br) in the presence of an alcohol, eg methanol.

The thiazole intermediates of formula XXI, wherein $R^7$ represents halogen (preferably Br) and $R^6$ represents hydrogen, may be prepared by reacting compounds of formula XXI, wherein $R^7$ represents said halogen and $R^6$ represents alkyl (preferably methyl) with LiOH in a suitable solvent, eg THF-$H_2O$.

Compounds of formula XXI, wherein $R^7$ represents said halogen and $R^6$ represents said alkyl may be prepared by reacting compounds of formula XXI, wherein $R^7$ represents $NH_2$ and $R^6$ represents said alkyl with TMSHa, wherein TMS represents trimethylsilyl and Ha represents said halogen, in the presence of *tert*-butylONO.

Compounds of formula XXI, wherein $R^7$ represents $NH_2$ and $R^6$ represents said alkyl may be prepared by reacting compounds of formula XX, wherein $R^6$ represents said alkyl and Ha represents halogen (preferably Br), with thiourea.

Compounds of formula XX may be prepared by reacting compounds of formula XVI with TMSHa (preferably TMSBr) in DMSO.

Compounds of formula II, XIII, XVI and XXII to XXV are known and/or may be prepared by conventional methods.

Pharmaceutically acceptable derivatives of the compounds of formula I include esters, amides, salts and hydrates. Salts of the compounds of formula I include metal ion salts, eg alkali metal and alkaline earth metal salts, and addition salts with suitable bases, eg suitable amines such as dicyclohexylamine and 1-adamantanamine.

"Alkyl" includes straight chain, branched, cyclic, saturated or unsaturated alkyl. "Hydroxyalkyl", "carboxyl", "alkoxy" and "carboxyalkoxy" are interpreted similarly.

The compounds of formula I may exist in enantiomeric forms, all enantiomers, racemates and mixtures thereof are included within the scope of the invention. The various optical isomers may be isolated by separation of a racemic mixture of the compounds using conventional

techniques, e.g. fractional crystallisation, or HPLC. Alternatively the individual enantiomers may be made by reaction of the appropriate optically active starting materials under reaction conditions which will not cause racemisation.

Intermediate compounds may also exist in enantiomeric forms and may be used as purified enantiomers, racemates or mixtures.

The compounds of formula I, and pharmaceutically acceptable salts, enantiomers and tautomers thereof, are useful because they possess pharmacological activity in animals. The invention therefore provides a compound of formula (I) as defined herein as a therapeutic agent. In particular, the compounds are useful as anti-inflammatory agents. The compounds are indicated for use in the treatment or prophylaxis of inflammatory conditions in mammals including man.

Conditions that may be specifically mentioned are:
osteoarthritis, rheumatoid arthritis, rheumatoid spondylitis, gouty arthritis and other arthritic conditions, inflamed joints;
eczema, psoriasis, dermatitis or other inflammatory skin conditions such as sunburn;
inflammatory eye conditions including uveitis and conjunctivitis;
lung disorders in which inflammation is involved, eg asthma, bronchitis, pigeon fancier's disease, farmer's lung, acute respiratory distress syndrome, bacteraemia, endotoxaemia (septic shock) and pancreatitis;
conditions of the gastrointestinal tract including aphthous ulcers, gingivitis, Crohn's disease (a condition of the small and sometimes also of the large intestine), atrophic gastritis and gastritis varialoforme (conditions of the stomach), ulcerative colitis (a condition of the large and sometimes of the small intestine), coeliac disease (a condition of the small intestine), regional ileitis (a regional inflammatory condition of the terminal ileum), peptic ulceration (a condition of the stomach and duodenum) and irritable bowel syndrome; pyresis, pain; damage to the gastrointestinal tract resulting from infections by, eg *Helicobacter* pylori, or treatments with non-steroidal anti-inflammatory drugs; and other conditions associated with inflammation, particularly those in which phospholipid, lipoxygenase and cyclooxygenase products are a factor.

For the above mentioned therapeutic indications, doses administered will, of course, vary with compound employed, the mode of administration and the treatment desired. However, in general, satisfactory results are obtained when the compound is administered at a daily

dosage of from about 0.1 mg to about 20 mg per kg of animal body weight, preferably given in divided doses 1 to 4 times a day or in sustained release form. For man the total daily dose is in the range of from 7.0 mg to 1400 mg and unit dosage forms suitable for oral administration comprise from 2.0 mg to 1400 mg of the compound admixed with a solid or liquid pharmaceutical diluent or carrier.

Topical administration of the compounds of invention or their pharmaceutically acceptable salts, enantiomers or tautomers is also contemplated.

The compounds of formula I may be used on their own or in the form of appropriate medicinal preparations for enteral, parenteral or topical administration.

For example there is provided a pharmaceutical composition comprising a compound of formula I, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier. The composition comprises preferably less than 80% and more preferably less than 50% by weight of the compound of formula I or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

Examples of such adjuvants, diluents and carriers are: for tablets and dragees - lactose, starch, talc, stearic acid; for capsules - tartaric acid or lactose; for injectable solutions - water, alcohols, glycerin, vegetable oils; for suppositories - natural or hardened oils or waxes.

Compositions in a form suitable for oesophageal administration include tablets, capsules and dragees; compositions in a form suitable for administration to the lung include aerosols, particularly pressurised aerosols; compositions in a form suitable for administration to the skin include creams, eg oil-in-water emulsions or water-in-oil emulsions; compositions in a form suitable for administration to the eye include drops and ointments.

In a further aspect the invention provides a method of treatment of the above disorders which comprises administering to the patient a compound of formula (I) as defined herein or a pharmaceutically acceptable salt, enantiomer or tautomer thereof. In a still further aspect the invention provides the use of a compound of formula (I) as defined herein in the manufacture of a medicament for the treatment of the above disorders.

The invention is illustrated by the following examples:

**EXAMPLE 1**

**2-[2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylic acid**

**a) (1,1-Dimethyl)ethyl 3-nitro-4-hydroxybenzoate**

A mixture of DCC (33.0g), (1,1-dimethyl)ethyl alcohol (300 ml) and 3-nitro-4-hydroxybenzoic acid (27.50g) in THF (150 ml) was treated with DMAP (0.5g) and stirred at 25°C for 18 hrs. A solid formed (DCU) which was filtered off and discarded. The filtrate was dissolved in ethyl acetate and hexane added to precipitate out further DCU which was removed by filtration. The filtrate was concentrated to a gum which was passed down a silica gel column eluted with hexane:ethyl acetate (9:1, v/v). The product was isolated as a solid (3.65g).

Mass spectrum : m/e 239

$^1$H NMR, $CDCl_3$, d: 1.61 (s, 9H), 1.19 (d, 1H,), 8.17-8.20 (dd, 1H), 8.74 (d, 1H).

**b) (1,1-Dimethyl)ethyl 3-amino-4-hydroxybenzoate**

A solution of the product from 1a (3.25g) in ethyl acetate (100 ml) was treated with 10%Pd/C (0.25g) and stirred under an atmosphere of hydrogen gas at 3 bar for 4 hrs. The reaction mixture was filtered through celite and evaporated to give the required product as a solid (2.84g).

Mass spectrum : m/e 209

$^1$H NMR, DMSO-$_{D6}$, d: 1.49 (s, 9H), 3.38 (bs, 2H), 4.73 (bs, 1H) 6.68 (d, 1H), 7.03-7.06 (dd, 1H), 7.17 (d, 1H).

**c) 5-Phenylpentyl mesylate**

5-Phenylpentanol (6.0g) and triethylamine (5.6 ml) were dissolved in dry THF (50 ml) and cooled to -5°C. A solution of methanesulphonic anhydride (6.7g) in dry THF (20 ml) was added dropwise. The reaction mixture was stirred at 25°C for 3 hrs and then evaporated. The residue was dissolved in ethyl acetate, washed with 2N hydrochloric acid, water, brine, dried ($MgSO_4$) and evaporated to give the product as an oil (7.3g).

Mass spectrum: m/e 326

NMR: $CDCl_3$ d: 1.45 (m, 2H), 1.67 (m, 4H), 1.78 (m, 2H), 2.63 (t, 2H), 2.98 (s, 3H), 4.24 (t, 2H), 7.18 (m, 3H), 7.29 (m, 2H).

**d) 4-(5-Phenylpentylthio)phenol**

5-Phenylpentyl mesylate (35.3g), 4-hydroxythiophenol (18.9g), caesium carbonate (47.6g) in acetonitrile were heated at reflux for 8 hrs. The mixture was then poured into water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$) and evaporated to give an oil. This was passed down a silica gel column eluted with hexane:ethyl acetate (5:1) to afford the product as a white solid, (33g).

NMR: $CDCl_3$ d: 1.43 (m, 2H), 1.60 (m, 2H), 2.59 (t, 2H), 2.8 (t, 2H), 4.83 (s, 1H), 7.17 (m, 3H), 7.27 (m, 2H).

**e) 2-[4-(5-Phenylpentylthio)phenoxy]acetonitrile**

4-(5-Phenylpentylthio)phenol (2.73g), bromoacetonitrile (1.44g) and caesium carbonate (4.8g) in acetonitrile (50 ml) were heated at reflux for 4 hrs, with stirring. The reaction mixture was allowed to cool to 25°C, poured into 2N hydrochloric acid (300 ml) and extracted with ethyl acetate. The combined organic extracts were washed with water, brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to give an oil. This was passed down a silica gel column eluted with hexane:dichloromethane (1:1, v/v). The appropriate fractions were collected and evaporated to give the required product as a clear colourless oil, (2.39g).

Mass spectrum m/e 311

$^1H$ NMR, $CDCl_3$ , d: 1.40-1.48 (m, 2H), 1.57-1.67 (m, 4H), 2.59 (t, 2H), 2.84 (t, 2H), 4.73 (s, 2H), 6.91 (d, 2H), 7.16 (m, 3H), 7.30 (m, 2H), 7.35 (d, 2H).

**f) 2-[4-(5-Phenylpentylthio)phenoxy]acetaldehyde**

A stirred solution of 2-[4-(5-phenylpentylthio)phenoxy]acetonitrile (2.0g) in dry toluene (10 ml) was cooled to -45°C under a nitrogen atmosphere. A 1M solution of Dibal-H in toluene (9.5 ml) was added dropwise and the resulting solution was allowed to warm to 0°C over 1 hr and stirred at this temperature for a further 1 hr. A saturated solution of ammonium chloride (15 ml) was added followed by diethyl ether (15 ml). A solution of concentrated sulphuric acid (6 ml) in water ( 24 ml) was then added and the mixture was stirred at 25°C for 18 hrs. The mixture was added to ethyl acetate (500 ml), the separated organic phase washed with water, brine, dried ($MgSO_4$) and the solvent was evaporated to give the product as a yellow oil, (1.66g).

Mass spectrum : m/e 314

$^1$H NMR, $CDCl_3$, d: 1.43-1.47 (m, 2H), 1.59-1.65 (m, 4H), 2.58 (t, 2H) 2.81 (t, 2H), 4.54 (s, 2H), 6.82 (d, 2H), 7.16 (m, 3H), 7.26 (m, 2H), 7.36 (d, 2H).

**g) 3-[4-(5-Phenylpentylthio)phenoxy]-2-hydroxypropionitrile**

2-[4-(5-Phenylpentylthio)phenoxy]acetaldehyde (1.56g), acetone cyanohydrin (0.7 ml) and triethylamine (1 drop) in dichloromethane (20 ml) were stirred at 25°C for 18 hrs. The solvent was evaporated to afford a yellow solid. The solid was passed down a silica gel column eluted with dichloromethane:methanol (50:1, v/v). The appropriate fractions were combined and evaporated to afford the required product as a white solid (0.95g).

$^1$H NMR, $CDCl_3$, d: 1.41-1.48 (m, 2H), 1.58-1.65 (m, 4H), 2.59 (t, 2H), 2.83 (t, 2H), 3.00 (d, 1H), 4.18-4.25 (m, 2H), 4.79-4.84 (m, 1H), 6.87 (d, 2H), 7.14-7.19 (m, 3H), 7.25-7.30 (m, 2H), 7.33 (d, 2H).

**h) 3-[4-(5-Phenylpentylthio)phenoxy]-2-hydroxy-1-ethoxy-1-iminopropane hydrochloride**

Ethanol (3.0g) in chloroform (25 ml) was cooled to 0°C and stirred under an atmosphere of nitrogen gas. Acetyl chloride (4.1g) was added and the mixture stirred at 0°C for 0.5 hr. (3-[4-(5-phenylpentylthio)phenoxy]-2-hydroxypropionitrile (0.94g) was added and the mixture was allowed to warm to 25°C over 1 hr and stirred at this temperature for a further 18 hrs. The solvent was evaporated to give the required product as a white solid (1). This was used directly in the next step.

**i) (1,1-Dimethyl)ethyl 2-[2-(4-(5-phenylpentylthio)phenoxy)-1-hydroxyethyl]benzoxazole-5-carboxylate**

The product from 1h (1.26g) and the product from 1b (0.85g) in acetonitrile (30 ml) were heated at reflux for 6 hrs. The reaction mixture was cooled to 25°C, poured into ethyl acetate (500 ml), washed with water, brine, dried ($MgSO_4$) and evaporated to give a gum. This was passed down a silica gel column eluted with hexane:ethyl acetate (4:1, v/v) to give the product as an oil, (1.20g).

$^1$H NMR, $CDCl_3$, d: 1.40-1.46 (m, 2H), 1.55-1.60 (m, 4H), 1.62 (s, 9H), 2.58 (t, 2H), 2.80 (t, 2H), 3.80 (d, 1H) 4.44-4.53 (m, 2H) 5.33-5.38 (m, 1H), 6.85 (d, 2H), 7.13-7.19 (m, 3H), 7.25-7.29 (m, 2H), 7.31 (d, 2H), 7.55 (d, 1H), 8.05-8.07 (dd, 1H), 8.39 (d, 1H).

**j) (1,1-Dimethyl)ethyl 2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylate**

The product from 1i (0.54g, 1 mmol) was dissolved in dichloromethane (25 ml), treated with Dess-Martin reagent (0.75g) and stirred at 25°C for 4 hrs. The reaction mixture was mixed with ethyl acetate (200 ml), washed with a 10% aqueous solution of sodium thiosulphate (3 x 200 ml), brine and dried ($MgSO_4$). The solvent was evaporated to give a yellow gum. This was passed down a silica gel column eluted with hexane:ethyl acetate (9:1) to give the product as a yellow solid, (0.23g).

Mass spectrum: m/e 550 ($M+NH_4$)

$^1$H NMR, $CDCl_3$ , d: 1.41-1.47 (m, 2H), 1.58-1.62 (m, 4H), 1.64 (s, 9H), 2.59 (t, 2H), 2.83 (t, 2H), 5.55 (s, 2H), 6.95 (d, 2H), 7.15-7.19 (m, 3H), 7.23-7.30 (m, 2H), 7.35 (d, 2H) 7.71 (d, 1H), 8.26 (dd, 1H), 8.57 (d, 1H).

**k) 2-[2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl] benzoxazole-5-carboxylic acid**

A solution of the product from 1j (0.2g) in formic acid (10 ml) and dichloromethane (5 ml) was stirred at 25°C for 3 hrs. Toluene (20 ml) was added and the mixture was evaporated. This procedure was repeated twice to afford a yellow solid which was recrystallised from acetonitrile to give the required product (0.09g).

Mass spectrum: m/e 474 (M-H)

M.p.: 148-149°C

$C_{27}H_{25}NO_5S$ requires: C 68.2 H 5.3 N 3.0 S 6.7 %
found: C 68.1 H 5.4 N 3.1 S 6.7 %

**EXAMPLE 2**

**1-Methyl-2-[2-[4-(5-phenylpentylthio)phenoxy]-1-oxoethyl]benzimidazole**

**a) Ethyl 2-[4-(5-phenylpentylthio)phenoxy]acetate**

4-(5-Phenylpentylthio)phenol (2.0g) was dissolved in acetonitrile (60 ml) and ethyl 2-bromoacetate (1.23g) was added. The mixture was treated with caesium carbonate (3.58g) and stirred at 25°C for 18 hrs. Water (50 ml) was added and the mixture was extracted with ethyl acetate. The combined extract was washed with saturated sodium bicarbonate, water, brine, dried ($MgSO_4$) and evaporated to give the product as a solid, (2.32g).

$^1$H NMR, $CDCl_3$ , d: 1.30 (t, 3H), 1.38-1.48 (m, 2H), 1.56-1.66 (m, 4H), 2.59 (t, 2H), 2.81 (t, 2H), 4.27 (q, 2H), 4.60 (s, 2H), 6.84 (d, 2H), 7.14-7.20 (dd, 2H), 7.25 (m, 3H), 7.32 (d, 2H).

b) 1-Methyl-2-[2-[4-(5-Phenylpentylthio)phenoxy]-1-oxoethyl]benzimidazole

A stirred solution of 1-Methylbenzimidazole (0.223g) in dry THF (30 ml) was cooled to -78°C under a nitrogen atmosphere. Butyl lithium (1.6M in hexane, 1.06 ml,) was added dropwise and the solution stirred at below -60°C for 15 mins. The ester prepared in 2a, (0.60g) in THF (10 ml) was added dropwise over 5 mins, and the reaction was stirred at below -60°C for 0.5 hr. Cooling was removed and the reaction was allowed to attain ambient temperature. Diethyl ether (100 ml) and 2N hydrochloric acid (50 ml) were added and the two layers separated. The aqueous layer was extracted with ether, the combined ether extract was washed with water, brine, dried ($MgSO_4$) and evaporated to a colourless oil. The oil was passed down a silica gel column eluted with hexane:ethyl acetate (4:1, v/v). The appropriate fractions were combined and evaporated to give a white solid which was recrystallised from acetonitrile to afford the product, (0.35g).

Mass spectrum: m/e 445 (M+H)
M.p.: 94-95°C

| | | | | | |
|---|---|---|---|---|---|
| $C_{27}H_{28}N_2O_2S$ | requires: | C 72.9 | H 6.4 | N 6.3 | S 7.2 % |
| | found: | C 73.0 | H 6.1 | N 6.4 | S 7.2 % |

**EXAMPLE 3**
**5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]thiazole**

a) 5-(2-(Dimethyl(1,1-dimethylethyl)silyloxy)ethyl)-4-methylthiazole

5-(2-Hydroxyethyl)-4-methylthiazole (15.0g) was dissolved in DMF (80 ml) and imidazole (7.15g) was added. The reaction was cooled to 0°C and t-butyldimethylsilylchloride (15.8g) in DMF (100 ml) was added dropwise over 1 hr. The reaction was stirred at 25°C for 18 hrs, water (100 ml) was added and the mixture was extracted with ethyl acetate. The extract was washed with water, dried (MgSO4) and evaporated to give an oil. This was passed down a silica gel column eluted with hexane:ethyl acetate (3:2, v/v) to give the product as a colourless oil (23.74g).

$^1$H NMR, $CDCl_3$ , d: 0.01 (s,6H), 0.87 (s, 9H), 2.39 (s, 3H), 2.94 (t, 2H), 3.76 (t, 2H), 8.55 (s, 1H).

**b) 5-(2-(Dimethyl(1,1-dimethylethyl)silyloxy)ethyl)-4-methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]thiazole**

Using the procedure described for example 2b but using the thiazole derivative prepared in example 3a, in place of 1-methylbenzimidazole led to the preparation of the required compound as an oil in 79% yield.

$^1$H NMR, $CDCl_3$ , d: 0.02 (s, 6H), 0.88 (s, 9H), 1.40-1.48 (m, 2H), 1.56-1.66 (m, 4H), 2.45 (s, 3H), 2.59 (t, 2H), 2.81 (t, 2H), 3.02 (t, 2H), 3.83 (t, 2H), 5.46 (s, 2H), 6.92 (d, 2H), 7.14-7.19 (dd, 2H), 7.26 (m, 3H), 7.31 (d, 2H).

**c) 5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]thiazole**

The silyl ether prepared in 3b (0.62g,) was dissolved in dry THF (5 ml) and treated with a 1M solution of TBAF in THF (3.3 ml). The mixture was stirred at 25°C for 1 hr. Water (70 ml) was added and the mixture was extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), evaporated and passed down a silica gel column eluted with ethyl acetate:hexane (1:1, v/v). The appropriate fractions were evaporated to a solid, which crystallised from ethyl acetate/hexane (0.12g).

Mass spectrum: m/e 456 (M+H)

M.p.: 68-69°C

$C_{25}H_{29}NO_3S_2$ requires: C 65.9 H 6.4 N 3.1 S 14.1 %

found: C 65.9 H 6.5 N 3.2 S 14.4 %

**EXAMPLE 4**

**6-Methoxy-2-[2-[4-(5-phenylpentylthio)phenoxy]-1-oxoethyl]benzothiazole**

**a) 6-Methoxybenzothiazole**

6-Hydroxybenzothiazole (0.246g) was dissolved in dry DMF (20 ml) and treated with sodium hydride (60% oil suspension, 0.072g). The mixture was stirred at 25°C for 10 min, treated with methyl iodide (0.23g) and stirring continued for 18 hrs. The reaction mixture was poured into 2N hydrochloric acid (100 ml) and extracted with ethyl acetate. The

extract was washed with water, brine, dried ($MgSO_4$) and evaporated to give the product as an oil, (0.25g).

$^1$H NMR, $CDCl_3$ , d: 3.90 (s, 3H), 7.11-7.15 (dd, 1H), 7.40 (d, 1H), 8.01 (d, 1H), 8.83 (s, 1H).

**b) 6-Methoxy-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]benzothiazole**

Using the procedure described for example 2b but using 6-methoxy-benzothiazole (4a) in place of 1-methylbenzimidazole led to the preparation of the required compound as a white solid in 48% yield.

Mass spectrum: m/e 478 (M+H)
M.p.: 84-86°C
$C_{27}H_{27}NO_3S_2$ requires: C 67.9 H 5.3 N 2.9 S 13.4 %
found: C 67.6 H 5.6 N 3.0 S 12.9 %

**EXAMPLE 5**
**1-Methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]imidazole**

**a) (1,1-Dimethyl)ethyl 2-[4-(phenylpentylthio)phenoxy]acetate**

Using the procedure described for example 2a but using (1,1-dimethyl)ethyl 2-bromoacetate in place of ethyl 2-bromoacetate gave the required product as a colourless oil in quantitative yield.

$^1$H NMR, $CDCl_3$ , d: 1.48 (s, 9H), 1.38-1.51 (m, 2H), 1.56-1.66 (m, 4H), 2.59 (t, 2H), 2.81 (t, 2H), 4.49 (s, 2H), 6.80-6.85 (d, 2H), 7.15-7.20 (m, 3H), 7.24-7.28 (m, 2H), 7.29-7.33 (d, 2H).

**b) 2-[4-(Phenylpentylthio)phenoxy]acetic acid**

The ester prepared in example 5a (5.33g) was dissolved in a mixture of formic acid (20 ml) and dichloromethane (80 ml) and stirred at 25°C for 24 hrs. The dichloromethane was evaporated under reduced pressure and the residue treated with water (30 ml). A white

precipitate formed which was collected by filtration, washed with water and dried in a vacuum desiccator to give the product as a white solid (4.08g).

$^1$H NMR, $CDCl_3$ , d: 1.38-1.48 (m, 2H), 1.49-1.67 (m, 4H), 2.56-2.62 (t, 2H), 2.80-2.85 (s, 2H), 4.66 (t, 2H), 6.83-6.88 (dd, 2H), 7.14-7.20 (m, 3H), 7.25-7.30 (m, 2H), 7.30-7.35 (d, 2H).

**c) N-[2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl]pyrrolidine**

2-[4-(Phenylpentylthio)phenoxy]acetic acid (4.08g) was dissolved in THF (50 ml) and cooled to 0°C. 1,1'-carbonyldiimidazole (2.20g) was added and the solution stirred at 0°C for 1.5 hrs. Pyrrolidine (0.97g) in THF (10 ml) was added dropwise while keeping the reaction temperature below 5°C. The ice-bath was then removed and the reaction was stirred at 25°C for 1.5 hrs. Ethyl acetate (200 ml) was added and the mixture was washed with 2N hydrochloric acid, water, saturated sodium bicarbonate, brine, dried ($MgSO_4$) and evaporated to a gum. The gum was passed down a silica gel column eluted with ethyl acetate :hexane (4:1, v/v) to afford the product as a colourless oil (4.06g, 86%).

Mass spectrum: m/e 384 (M+H)

$C_{23}H_{29}NO_2S$ requires: C 72.0 H 7.6 N 3.7 S 8.3 %
found: C 71.7 H 7.6 N 3.7 S 8.2 %

**d) 1-Methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]imidazole**

A stirred solution of 1-methylimidazole (0.12g) in dry THF (10 ml) was cooled to -78°C under a nitrogen atmosphere. Butyl lithium (1.6M in hexane, 0.93 ml) was added dropwise and the solution stirred at below -60°C for 15 mins. The amide prepared in 5c, (0.515g) in THF (10 ml) was added dropwise over 5 mins, keeping the temperature below -60°C. The reaction was allowed to attain ambient temperature and stirred at 25°C for 0.5 hr. Diethyl ether (20 ml) and 2N hydrochloric acid (50 ml) were added and the two layers separated. The aqueous layer was extracted with ether (2 x 30 ml) and the combined ether extract was washed with water, dried ($MgSO_4$) and evaporated to a colourless oil which solidified on standing (0.46g). The solid re-crystallised from ethyl acetate/hexane.

Mass spectrum: m/e 395 (M+H)
M.p.: 76-77°C

$C_{23}H_{26}N_2O_2S$ requires: C 70.0 H 6.6 N 7.1 S 8.1 %
found: C 69.7 H 6.7 N 7.0 S 7.8 %

**EXAMPLE 6**

**2-[2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl]benzothiazole**

Using the procedure described for example 5d but using benzothiazole in place of 1-methylimidazole led to the preparation of the required compound as a white solid in 43% yield.

Mass spectrum: m/e 448 (M+H)
M.p.: 91-92°C
$C_{26}H_{25}NO_2S_2$ requires: C 69.8 H 5.6 N 3.1 S 14.3 %
found: C 69.6 H 5.7 N 3.3 S 14.3 %

**EXAMPLE 7**

**2-[2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl]thiazole**

Using the procedure described for example 5d but using 2-bromothiazole in place of 1-methylimidazole led to the preparation of the required compound as a white solid in 34% yield.

Mass spectrum: m/e 398 (M+H)
M.p.: 74-75°C
$C_{22}H_{23}NO_2S_2$ requires: C 66.5 H 5.8 N 3.5 S 16.1 %
found: C 66.8 H 5.9 N 3.7 S 16.0 %

**EXAMPLE 8**

**2-[2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl]benzothiazole-6-carboxylic acid**

Benzothiazole-6-carboxylic acid (0.483g) was dissolved in dry THF (30 ml) and cooled to -78°C under a nitrogen atmosphere. A 1.6 M solution of butyl lithium in hexane (3.7 ml) was added dropwise and the reaction mixture was stirred at -70°C for 0.5 hr. A solution of the amide prepared in example 5c, (0.517g) in dry THF (10 ml) was added dropwise and the reaction was stirred for a further 0.75 hr. The cooling bath was removed, the reaction was allowed to warm to 0°C and treated with a saturated aqueous solution of ammonium

chloride (50 ml). The mixture was extracted with ethyl acetate and the extract was washed with water, brine, dried ($MgSO_4$) and evaporated to give the crude product as a solid. This was passed down a silica gel column eluted with hexane:ethyl acetate (1:1, v/v) to give the product as a yellow solid, (0.15g).

| | | |
|---|---|---|
| Mass spectrum: m/e | 492 (M+1) | |
| M.p.: 107-171°C | | |
| $C_{27}H_{25}NO_4S$ | requires: | C 66.0; H 5.1; N 2.9; S13.0% |
| | found: | C 66.2; H 5.2; N 3.0; S12.9 % |

**EXAMPLE 9**

**4-Methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]thiazole-5-carboxylic acid**

**a) Ethyl 2-bromo-4-methylthiazole-5-carboxylate**

A solution of (1,1-dimethyl)ethane-2-nitrite (2.5 ml) in acetonitrile (100 ml) was cooled in an ice-bath and treated with the dropwise addition of trimethylsilyl bromide (2.8 ml). After addition was complete the mixture was stirred at 0°C for 20 mins. Ethyl 2-amino-4-methylthiazole-5-carboxylate (2.0 g), dissolved in a mixture of acetonitrile (75 ml) and ethyl acetate (25 ml), was added dropwise, over 40 min while maintaining the temperature at 0°C. The cooling bath was removed and the mixture was stirred at 25°C for 18 hrs. The solvent was removed under reduced pressure and the residue was passed down a silica gel column eluted with ethyl acetate:hexane (2:1) to afford the product as an orange-red oil (1.88g).

Mass spectrum: m/e 250 / 252 (M+1)

$^1H$ NMR, $CDCl_3$ , d: 1.36 (t, 3H), 2.71 (s, 3H), 4.33 (q, 2H).

**b) 2-Bromo-4-methylthiazole-5-carboxylic acid**

The thiazole prepared in 9a (1.88g,) was dissolved in a mixture of THF (40 ml) and water (10 ml). Lithium hydroxide monohydrate (1.58g,) was added and the mixture was stirred at 25°C for 18hrs. The reaction mixture was then poured into 2N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, brine, dried ($MgSO_4$) and evaporated to afford the product as a white solid, (1.64g).

Mass spectrum: m/e 293 / 295 (TMS-ester)
$^1$H NMR, DMSO$_{D6}$ , d: 2.60 (s, 3H).

**c) 4-Methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]thiazole-5-carboxylic acid**

Using the procedure described for example 8 but using 2-bromo-4-methyl-thiazole-5-carboxylic acid in place of benzothiazole-6-carboxylic acid led to the preparation of the required compound as a white solid in 71% yield.

Mass spectrum: m/e 456 (M+1)
M.p.: 142-3°C

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_{24}H_{25}NO_4S_2$ | requires: | C 63.3 | H 5.5 | N 3.1 | S 14.1 | % |
| | found: | C 63.0 | H 5.4 | N 3.2 | S 13.8 | % |

**EXAMPLE 10**

**4-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid**

**a) Methyl 5-bromo-6-oxo-heptanoate**

Methyl 6-oxo-heptanoate (5.22g) in dry acetonitrile (50 ml) was treated with slow addition of TMSBr (5.05g) followed by slow addition of DMSO (2.58g). During the additions the reaction temperature was kept below 20°C by cooling in an ice-bath. The mixture was then stirred at ambient temperature for 18 hrs, poured into water and extracted with ether. The ether extract was washed with water, brine, dried ($MgSO_4$) and evaporated to an oil which was purified by a silica gel column eluted with hexane:ethyl acetate (5:1, v/v). The appropriate fractions were evaporated to afford the product as a clear oil (4.0g).

Mass spectrum : m/e 236 / 238
$^1$H NMR, $CDCl_3$, d: 1.6-2.2 (m, 4H), 2.36 (s, 3H,), 2.38(t, 2H), 3.7 (s, 3H) 4.24 (dd, 1H).

**b) Methyl 4-(2-amino-4-methylthiazol-5-yl)butanoate hydrobromide**

Methyl 5-bromo-6-oxoheptanoate (1.16g) was dissolved in ethanol (50 ml) and treated with thiourea (0.373g).The mixture was heated at reflux for 4 hrs and the solvent was removed under reduced pressure to give the product as a white solid (1.44g).

Mass spectrum : m/e 214

$^1$H NMR, $CDCl_3$, d: 1.81-1.91 (m, 2H), 2.20 (s, 3H), 2.36 (t, 2H), 2.60 (t, 2H), 3.69 (s, 3H), 8.80 (bs, 3H).

**c) Methyl 4-(2-bromo-4-methylthiazol-5-yl)butanoate**

Using the procedure described in 9a, with the 2-aminothiazole derivative prepared in 10b, led to the required product as an orange-red oil in 33% yield.

Mass spectrum : m/e 277 / 279

$^1$H NMR, $CDCl_3$, d: 1.87-1.98 (m, 2H), 2.31 (s, 3H), 2.36 (t, 2H), 2.75 (t, 2H), 3.67 (s, 3H).

**d) 4-(2-Bromo-4-methylthiazol-5-yl)butanoic acid**

Using the procedure described in 9b, with the 2-bromothiazole derivative prepared in 10c, led to the required product as a white solid in 73% yield.

Mass spectrum : m/e 264 / 266 (M+1)

$^1$H NMR, $CDCl_3$, d: 1.88-1.98 (m, 2H), 2.32 (s, 3H), 2.42 (t, 2H), 2.78 (t, 2H).

**e) 4-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid**

Using the procedure described for example 8 but using 4-(2-bromo-4-methylthiazol-5-yl)butanoic acid in place of benzothiazole-6-carboxylic acid led to the preparation of the required compound as a white solid in 33% yield.

Mass spectrum: m/e 498 (M+1)

M.p.: 97-98°C

$C_{27}H_{31}NO_4S_2$ requires: C 65.2 H 6.3 N 2.8 S 12.9 %

found: C 65.2 H 6.4 N 2.8 S 12.7 %

**EXAMPLE 11**

**2-[2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl]thiazole**

**a) 4-[3,5-Dichlorobenzyloxy]phenol**

Quinol (4.9g) was dissolved in dry DMF (100 ml) and treated with caesium carbonate (14.6g). 3,5-Dichlorobenzylchloride (2.9g) was added and the mixture was stirred at 25°C for 72 hrs. The mixture was poured into 2N hydrochloric acid (250 ml) and extracted with ethyl acetate. The extract was washed with water, brine, dried ($MgSO_4$), evaporated and the residue passed down a silica gel column eluted with hexane:ethyl acetate (5:1, v/v). The appropriate fractions were combined and evaporated to give the product as a white solid, (2.41g).

Mass spectrum : m/e 268 / 270 / 272

$^1$H NMR, $CDCl_3$, d: 4.55 (s, 1H), 4.95 (s, 2H), 6.75-6.85 (m, 4H)
7.31 (s, 3H).

**b) Ethyl 2-[4-(3,5-dichlorobenzyloxy)phenoxy]acetate**

The procedure described in example 2a was used with ethyl 2-bromoacetate and 4-(3,5-dichlorobenzyloxy)phenol to give the product as a white solid in 98% yield.

Mass spectrum : m/e 354 / 356 / 358

$^1$H NMR, $CDCl_3$, d: 1.30 (t, 3H), 4.3 (q, 2H), 4.58 (s, 2H), 4.96 (s, 2H)
6.89 (s, 4H), 7.31 (s, 3H).

**c) 2-[2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl]thiazole**

The procedure described in example 2b was used with 2-bromothiazole and ethyl 2-[4-(3,5-dichlorobenzyloxy)phenoxy]acetate to give the product as a white solid in 32% yield.

Mass spectrum: m/e 394 / 396 / 398 (M+1)

M.p.: 116-118°C

| | | |
|---|---|---|
| $C_{18}H_{13}Cl_2NO_3S$ | requires: | C 54.8 H 3.3 N 3.6 S 8.1 % |
| | found: | C 54.9 H 3.3 N 3.8 S 7.9 % |

**EXAMPLE 12**

**5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl]thiazole**

**a) 5-(2-(Dimethyl(1,1-dimethylethyl)silyloxy)ethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl]thiazole**

The procedure described in example 2b was used with the thiazole prepared in 3a and ethyl 2-[4-(3,5-dichlorobenzyloxy)phenoxy]acetate to give the product as a yellow gum in 32% yield.

Mass spectrum: m/e 566 / 568 / 570 (M+1)

$^1$H NMR, $CDCl_3$, d: 0.02 (s, 6H), 0.88 (s, 9H), 2.44 (s, 3H), 3.02 (t, 2H), 3.82 (t, 2H), 4.95 (s, 2H), 5.43 (s, 2H), 6.8-7.0 (m, 4H), 7.31 (s, 3H).

**b) 5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl]thiazole**

The product from 12a (0.36g) was dissolved in ethanol (10 ml), treated with pyridinium p-toluenesulfonate (0.08g) and water (0.25 ml) and the reaction was heated at 60°C for 8 hrs. The solvent was evaporated under reduced pressure and the residue was dissolved in ethyl acetate (100 ml), washed with water, brine, dried ($MgSO_4$) and evaporated. The residue was purified by passing down a silica gel column eluted with ethyl acetate:hexane (1:1, v/v) to give the product as a white solid which crystallised from ethyl acetate/hexane (0.18g).

Mass spectrum: m/e 452 / 454 / 456 (M+1)

M.p.: 115-116°C

$^1$H NMR, $CDCl_3$, d: 1.64 (bs, 1H), 2.45 (s, 3H), 3.08 (t, 2H), 3.91 (m, 2H), 4.96 (s, 2H), 5.43 (s, 2H), 6.8-7.0 (m, 4H), 7.31 (s, 3H).

**EXAMPLE 13**

**5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(decylsulfonyl)phenoxy)-1-oxoethyl]thiazole**

**a) 4-(Decylthio)phenol**

A solution of decyl bromide (11.5 ml) and 4-hydroxythiophenol (7g) in acetonitrile (100 ml) was treated with caesium carbonate (18g) and stirred at 25°C for 18 hrs. The reaction was poured into 2N hydrochloric acid (500 ml) and the product was extracted into ethyl acetate. The extract was washed with water, brine, dried ($MgSO_4$) and evaporated under reduced pressure to give the product as a solid (12.5g).

Mass spectrum: m/e 266
M.p.: 81-82°C

| | | | | |
|---|---|---|---|---|
| $C_{16}H_{26}OS$ | requires: | C 72.1 | H 9.8 | N 12.0 % |
| | found: | C 72.2 | H 9.9 | N 12.1 % |

**b) 4-(Decylsulfonyl)phenol**

4-(Decylthio)phenol (5.31g) was dissolved in acetone (500 ml). Water (100 ml) was added and the solution was cooled in an ice-bath. Oxone (15g) was added, the ice-bath was removed and the mixture was stirred at 25°C for 18 hrs. A 10% aqueous solution of sodium metabisulphite (1 lt) was added and the mixture was stirred for a further 1hr. The mixture was extracted with ethyl acetate and the extract was washed with water, brine, dried ($MgSO_4$) and evaporated to give a clear oil, (5.65g).

Mass spectrum: m/e 297 (M-1)
$^1$H NMR, $CDCl_3$, d: 0.87 (t, 3H), 1.2-1.3 (m, 12H), 1.35 (m, 2H), 1.67 (m, 2H), 3.06 (m, 2H), 6.56 (bs, 1H), 6.96 (d, 2H), 7.75 (d, 2H).

**c) Ethyl 2-[4-(decylsulfonyl)phenoxy]acetate**

The procedure described in example 2a was used with ethyl 2-bromoacetate and 4-(decylsulfonyl)phenol to give the required product as a white solid in 78% yield.

Mass spectrum : m/e 385 (M+1)

$^1$H NMR, $CDCl_3$, d: 0.87 (t, 3H), 1.23 (m, 14H), 1.31 (t, 3H), 1.64-1.74 (m, 2H), 3.02-3.07 (m, 2H), 4.29 (q, 2H), 4.70 (s, 2H), 7.00-7.04 (d, 2H), 7.82-7.86 (d, 2H).

**d) 5-(2-(Dimethyl(1,1-dimethylethyl)silyloxy)ethyl)-4-methyl-2-[2-(4-(decylsulfonyl)phenoxy)-1-oxoethyl]thiazole**

The procedure described in example 2b was used with the thiazole prepared in 3a and ethyl 2-[4-(decylsulfonyl)phenoxy]acetate to give the product as a colourless gum in 20% yield.

$^1$H NMR, $CDCl_3$, d: 0.02 (s, 6H), 0.87 (s, 12H), 1.2-1.3 (m, 12H), 1.35 (m, 2H), 1.69 (m, 2H), 2.46 (s, 3H), 3.05 (m, 4H), 3.84 (t, 2H), 5.57 (s, 2H), 7.07 (d, 2H), 7.83 (d, 2H).

**e) 5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(decylsulfonyl)phenoxy)-1-oxoethyl]thiazole**

The procedure described in example 12b was used with the product of 13d to give the product as white solid, which analysed as a monohydrate.

Mass spectrum: m/e 482 (M+1)

M.p.: 53-55°C

| | | | | | |
|---|---|---|---|---|---|
| $C_{24}H_{35}NO_5S_2.H_2O$ | requires: | C 57.7 | H 7.5 | N 2.8 | S 12.8 % |
| | found: | C 57.9 | H 7.4 | N 2.8 | S 12.7 % |

**EXAMPLE 14**

**5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(benzyloxy)phenoxy)-1-oxoethyl]thiazole**

**a) Ethyl 2-[4-(benzyloxy)phenoxy]acetate**

The procedure described in example 2a was used with ethyl 2-bromoacetate and 4-(benzyloxy)phenol to give the required product as a white solid in 78% yield.

Mass spectrum : m/e 286

$^1$H NMR, $CDCl_3$, d: 1.29 (t, 3H), 4.26 (q, 2H)), 4.56 (s, 2H), 5.01 (s, 2H)., 6.84-6.92 (m, 4H), 7.29-7.44 (m, 5H).

**b) 5-(2-(Dimethyl(1,1-dimethylethyl)silyloxy)ethyl)-4-methyl-2-[2-(4-(benzyloxy)phenoxy)-1-oxoethyl]thiazole**

The procedure described in example 2b was used with the thiazole prepared in 3a and ethyl 2-[4-(benzyloxy)phenoxy]acetate to give the product as a pale yellow gum in 67% yield.

$^1$H NMR, $CDCl_3$, d: 0.02 (s, 6H), 0.87 (s, 9H), 2.44 (s, 3H), 3.01 (t, 2H), 3.82 (t, 2H), 5.01 (s, 2H), 5.42 (s, 2H), 6.8-7.0 (m, 4H), 7.3-7.5 (m, 5H).

**c) 5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(benzyloxy)phenoxy)-1-oxoethyl]thiazole**

The procedure described in example 12b was used with the product of 14b to give the product as white solid in 64% yield.

Mass spectrum: m/e 384 (M+1)
M.p.: 109-110°C

| | | | | | |
|---|---|---|---|---|---|
| $C_{21}H_{21}NO_4S$ | requires: | C 65.8 | H 5.5 | N 3.7 | S 8.4 % |
| | found: | C 66.2 | H 5.6 | N 3.8 | S 8.4 % |

**EXAMPLE 15**

**5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(benzylthio)phenoxy)-1-oxoethyl]thiazole**

**a) 4-(Benzylthio)phenol**

The procedure described in example 13a was used with 4-hydroxythiophenol and benzyl chloride to give the required product as a white solid in 48% yield.

Mass spectrum : m/e 215 (M-1)
$^1$H NMR, $CDCl_3$, d: 3.97 (s, 2H), 4.92 (s, 1H), 6.73 (d, 2H), 7.25 (m, 7H).

**b) Ethyl 2-[4-(benzylthio)phenoxy]acetate**

The procedure described in example 2a was used with ethyl 2-bromoacetate and 4-(benzylthio)phenol to give the required product as a white solid in 90% yield.

Mass spectrum : m/e 302 (M+)

$^1$H NMR, $CDCl_3$, d: 1.29 (t, 3H), 3.99 (s, 2H), 4.26 (q, 2H), 4.58 (s, 2H), 6.8 (d, 2H), 7.25 (m, 7H).

**c) 5-(2-(Dimethyl(1,1-dimethylethyl)silyloxy)ethyl)-4-methyl-2-[2-(4-(benzylthio)phenoxy)-1-oxoethyl]thiazole**

The procedure described in example 2b was used with the thiazole prepared in 3a and ethyl 2-[4-(benzylthio)phenoxy]acetate to give the product as an yellow-orange gum 95% yield.

Mass spectrum : m/e 514 (M+)

$^1$H NMR, $CDCl_3$, d: 0.05 (s, 6H), 0.88 (s, 9H), 2.45 (s, 3H), 3.0 (t, 2H), 3.83 (t, 2H), 3.99 (s, 2H), 5.44 (s, 2H), 6.88 (d, 2H), 7.27 (m, 7H).

d) 5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(benzylthio)phenoxy)-1-oxoethyl)thiazole

The procedure described in example 12b was used with the product of 15c to give the product as white solid in 45% yield.

Mass spectrum: m/e 400 (M+1)
M.p.: 103-4°C

| | | |
|---|---|---|
| $C_{21}H_{21}NO_3S_2$ | requires: | C 63.1 H 5.3 N 3.5 S 16.1 % |
| | found: | C 62.8 H 5.2 N 3.6 S 16.2% |

**EXAMPLE 16**

**5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzylthio)phenoxy)-1-oxoethyl]thiazole**

a) 4-[3,5-Dichloro(benzylthio)]phenol

The procedure described in example 13a was used with 4-thiophenol and 3,5-dichlorobenzylchloride to give the required product as a colourless oil in 97% yield.

Mass spectrum : m/e 283 / 285 / 287 (M-1)
$^1$H NMR, $CDCl_3$, d: 2.05 (s, 1H), 3.86 (s, 2H), 6.75 (d, 2H), 6.91 (d, 2H), 7.20 (m, 3H).

b) Ethyl 2-[4-(3,5-dichlorobenzylthio)phenoxy]acetate

The procedure described in example 2a was used with ethyl 2-bromoacetate and 4-[3,5-Dichloro(benzylthio)]phenol to give the required product as a colourless oil in 78% yield.

Mass spectrum : m/e 370 / 372 / 374 (M+)
$^1$H NMR, $CDCl_3$, d: 1.29 (t, 3H), 3.88 (s, 2H), 4.27 (q, 2H), 4.59 (s, 2H), 6.82 (d, 2H), 7.03 (d, 2H), 7.22 (m, 3H).

**c) 5-(2-(Dimethyl(1,1-dimethylethyl)silyloxy)ethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzylthio)phenoxy)-1-oxoethyl]thiazole**

The procedure described in example 2b was used with the thiazole prepared in 3a and ethyl 2-[4-(3,5-dicholrobenzylthio)phenoxy]acetate to give the product as a pale yellow oil in 99% yield.

Mass spectrum : m/e 582 / 584 / 586 (M+1)
$^1$H NMR, $CDCl_3$, d: 0.04 (s, 6H), 0.88 (s, 9H), 2.45 (s, 3H), 3.02 (t, 2H), 3.82 (t, 2H), 3.88 (s, 2H), 5.46 (s, 2H), 6.9 (d, 2H), 7.25 (m, 7H).

**d) 5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzylthio)phenoxy)-1-oxoethyl)thiazole**

The procedure described in example 12b was used with the product of 16c to give the product as white solid in 57% yield. This analysed as the hemi-hydrade.

Mass spectrum: m/e 468 / 470 / 472 (M+1)
M.p.: 99-100°C

| | | |
|---|---|---|
| $C_{21}H_{19}Cl_2NO_3S_2 \cdot \frac{1}{2}H_2O$ | requires: | C 52.8 H 4.1 N 2.9 S 13.4% |
| | found: | C 52.9 H 4.0 N 2.9 S 13.0 % |

**EXAMPLE 17**

**1-Methyl-2-[2-(4-(5-phenylpentylsulfonyl)phenoxy)-1-oxoethyl]benzimidazole**

1-Methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]benzimidazole (0.075g) was dissolved in a mixture of acetone (5 ml) and water (1 ml). Oxone (0.15g) was added and the mixture was stirred at 25°C for 18 hrs. A 10% aqueous solution of sodium thiosulphate (50 ml) was added and the mixture was stirred for a further 0.5 hr. The mixture was extracted with ethyl acetate and the extract was washed with 10% sodium thiosulphate solution, water, brine, dried ($MgSO_4$) and evaporated to give a white solid (0.058g) which recrystallised from acetonitrile.

Mass spectrum: m/e 477 (M+1)
M.p.: 149-150 °C

$^1$H NMR, $CDCl_3$, d: 1.4 (m, 2H), 1.5-1.8 (m, 4H), 2.58 (t, 2H), 3.04 (m, 2H), 4.18 (s, 3H), 5.77 (s, 2H), 7.1-7.3 (m, 7H), 7.4-7.6 (m, 3H), 7.8-8.0 (m, 3H).

**EXAMPLE 18**

**2-[2-(4-(5-Phenylpentylsulfonyl)phenoxy)-1-oxoethyl]benzothiazole**

The procedure described in example 17 was used with 2-[2-(4-(phenylpentylthio)phenoxy)-1-oxoethyl]benzothiazole to give the product as a white solid in 65% yield.

Mass spectrum: m/e 480 (M+1)
M.p.: 127-8°C

| | | |
|---|---|---|
| $C_{27}H_{28}N_2O_4S$ | requires: | C 65.1 H 5.3 N 2.9 S 13.4 % |
| | found: | C 64.9 H 5.1 N 2.9 S 13.0 % |

**EXAMPLE 19**

**2-[2-(4-(5-Phenylpentylsulfonyl)phenoxy)-1-oxoethyl]-6-methoxybenzothiazole**

The procedure described in example 17 was used with 2-[2-(4-(phenylpentylthio)phenoxy)-1-oxoethyl]-6-methoxybenzothiazole to give the product as a solid in 60% yield.

Mass spectrum: m/e 510 (M+1)
M.p.: 109-110°C

| | | |
|---|---|---|
| $C_{26}H_{25}NO_4S_2$ | requires: | C 63.6 H 5.3 N 2.8 S 12.6 % |
| | found: | C 64.6 H 5.5 N 2.9 S 12.7 % |

**EXAMPLE 20**

**5-(2-Hydroxyethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzylsulfonyl)phenoxy)-1-oxoethyl]thiazole**

The procedure described in example 17 was used with 5-(2-hydroxyethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzylthio)phenoxy)-1-oxoethyl]thiazole to give the product as a solid in 69% yield.

Mass spectrum: m/e 500 / 502 / 504 (M+1)
M.p.: 116-7°C

| | | |
|---|---|---|
| $C_{21}H_{19}Cl_2NO_5S_2$ | requires: | C 50.4 H 3.8 N 2.8 S 12.8 % |
| | found: | C 49.9 H 3.7 N 2.7 S 13.2% |

**EXAMPLE 21**

**2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-oxoethyl]benzoxazole**

**a) 4-(3,4-Dichlorobenzylthio)phenol**

The procedure described in example 13a was used with 4-thiophenol and 3,4-dichlorobenzylchloride to give the required product as a yellow solid in quantitative yield.

Mass spectrum: m/e 283 / 285 / 287
NMR: $CDCl_3$ d: 3.87 (s, 2H), 4.91 (s, 1H), 6.74 (d, 2H), 6.96 (dd, 1H), 7.19 (d, 2H), 7.2-7.5 (m, 2H).

**b) 2-[4-(3,4-Dichlorobenzylthio)phenoxy]acetonitrile**

The procedure described in example 1e was used with 2-bromoacetonitrile and 4-(3,4-dichlorobenzylthio)phenol to give the required product as a yellow oil in 71% yield.

Mass spectrum: m/e 323 / 325 / 327
NMR: $CDCl_3$ d: 3.94 (s, 2H), 4.76 (s, 2H), 6.90 (d, 2H), 7.02 (d, 1H), 7.27-7.35 (m, 4H).

**c) 2-[4-(3,4-Dichlorobenzylthio)phenoxy]acetaldehyde**

The procedure described in example 1f was used with the product of 21b to give the required product as a colourless oil in 50% yield. This was used directly in the next step.

NMR: $CDCl_3$ d: 3.90 (s, 2H), 4.56 (s, 2H), 7.2-7.35 (m, 7H), 9.85 (s, 1H).

**d) 3-[4-(3,4-Dichlorobenzylthio)phenoxy]-2-hydroxypropionitrile**

The procedure described in example 1g was used with the product from 21c to give the required product as a colourless oil in 74% yield.

NMR: $CDCl_3$ d: 3.04 (d, 1H), 3.91 (s, 2H), 4.4-4.5 (m,2H), 4.82 (m, 1H), 6.84 (d, 2H), 6.99 (dd, 1H), 7.23-7.28 (m, 3H), 7.32 (d, 1H).

**e) 3-[4-(3,4-Dichlorobenzylthio)phenoxy]-2-hydroxy-1-ethoxy-1-iminopropane hydrochloride**

The procedure described in example 1h was used with the product from 21d to give the required product as a white solid in 93% yield. This was used directly in the next step.

NMR: $DMSO_{D6}$ d: 1.29 (t, 3H), 4.12 (s, 2H), 4.21 (d, 2H), 4.47(m, 2H), 4.81 (s, 1H), 6.88 (d, 2H), 7.2-7.3 (m,3H), 7.46 (d, 1H), 7.53 (d, 1H).

**f) 2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-hydroxyethyl]benzoxazole**

The procedure described in example 1i was used with the product from 21e and 2-aminophenol to give the required product as a yellow solid in 64% yield.

Mass spectrum: m/e 446 / 448 / 450 (M+1)

NMR: $CDCl_3$ d: 3.41 (d, 1H), 3.88 (s, 2H), 4.47 (m, 2H), 5.35 (m, 1H), 6.84 (d, 2H), 6.94 (dd, 1H), 7.18-7.32 (m, 6H), 7.75 (m, 1H), 8.57 (m, 1H).

**g) 2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-oxoethyl] benzoxazole**

The procedure described in example 1j was used with the product from 21h to give the required product as a yellow solid in 80% yield.

Mass spectrum: m/e 444 / 446 / 448 (M+1)

M.p.: 122-123°C

$C_{22}H_{15}Cl_2NO_3S$ requires: C 59.5 H 3.4 N 3.2 S 7.2 %

found: C 59.4 H 3.4 N 3.4 S 7.4 %

**EXAMPLE 22**

**2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-oxoethyl] benzimidazole**

**a) 2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-hydroxyethyl]benzimidazole**

The procedure described in example 1i was used with the product from 21e and 2,3-diaminobenzene to give the required product as a yellow solid in 65% yield.

Mass spectrum: m/e 445 / 447 / 449 (M+1)

NMR: $CDCl_3$ d: 3.89 (s, 2H), 4.26 (dd, 1H), 4.57 (dd, 1H), 5.42 (q, 1H), 6.88 (d, 2H), 6.97 (dd, 1H), 7.20-7.31 (m, 8H), 7.61 (m, 2H).

**b) 2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-oxoethyl]benzimidazole**

The procedure described in example 1j was used with the product from 22a to give the required product as a white solid in 56% yield which analysed as a hemihydrate.

Mass spectrum : m/e 443 / 445 / 447 (M+1)

M.p.: 141-142°C

$C_{22}H_{16}Cl_2N_2O_2S \cdot 0.5H_2O$ requires: C 58.4 H 3.8 N 6.2 S 7.1 %

found: C 58.8 H 3.7 N 6.2 S 7.1 %

**EXAMPLE 23**

**2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-oxoethyl]-6-methoxy benzoxazole**

**a) 2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-hydroxyethyl]-6-methoxybenzoxazole**

The procedure described in example 1i was used with the product from 21e and 2-amino-5-methoxyphenol to give the required product as a yellow solid in 57% yield.

Mass spectrum: m/e 476 / 478 / 480 (M+1)

M.p.: 87-88°C

$C_{23}H_{19}NCl_2O_4S$ requires: C 58.0 H 4.0 N 2.9 S 6.7 %

found: C 58.1 H 4.0 N 3.0 S 6.9 %

**b) 2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-oxoethyl]-6-methoxybenzoxazole**

The procedure described in example 1j was used with the product from 23a to give the required product as a yellow solid in 84% yield.

Mass spectrum: m/e 474 / 476 / 478 (M+1)
M.p.: 136-137 °C

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_{23}H_{17}NCl_2O_4S$ | requires: | C 58.2 | H 3.6 | N 3.0 | S 6.8 % |
| | found: | C 57.9 | H 3.6 | N 3.2 | S 6.7 % |

**EXAMPLE 24**
**2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylic acid**

**a) (1,1-Dimethyl)ethyl 2-[2-(4-(3,4-dichlorobenzylthio)phenoxy)-1-hydroxyethyl]benzoxazole-5-carboxylate.**

The procedure described in example 1i was used with the product from 21e and product from 1b to give the required product as a yellow solid in 61% yield.

NMR: $CDCl_3$ d: 1.62 (s, 9H), 3.32 (d, 1H), 3.88 (s, 2H)
4.49 (m, 2H), 5.36 (m, 1H), 6.84 (d, 2H),
6.97 (dd, 1H), 7.2-7.31 (m, 4H), 7.56 (d, 1H),
8.08 (dd, 1H), 8.39 (d, 1H).

**b) (1,1-Dimethyl)ethyl 2-[2-(4-(3,4-dichlorobenzylthio)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylate.**

The procedure described in example 1j was used with the product from 24a to give the required product as a yellow solid in 66% yield.

NMR: $CDCl_3$ d: 1.60 (s, 9H), 3.91 (s, 2H), 5.55 (s, 2H),
6.92 (d, 2H), 6.98 (dd, 1H), 7.23-7.32 (m, 4H),
7.72 (d, 1H), 8.26 (dd, 1H), 8.57 (d, 1H).

c) 2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylic acid

The procedure described in example 1k was used with the product from 24b to give the required product as a white solid in 56% yield which analysed as a monohydrate.

Mass spectrum: m/e 488 / 490 / 492 (M+1)
M.p.: 174-175°C

| | | |
|---|---|---|
| $C_{23}H_{15}NCl_2O_5S.H_2O$ | requires: | C 54.6 H 3.4 N 2.8 S 6.3 % |
| | found: | C 54.2 H 3.2 N 2.9 S 6.1 % |

EXAMPLE 25

2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-oxoethyl]benzoxazole-6-carboxylic acid

a) Propen-3-yl 3-hydroxy-4-aminobenzoate

3-Hydroxy-4-aminobenzoic acid (1.0g) was suspended in propen-3-ol (20 ml) and trimethylsilyl chloride (3.3 ml) was added dropwise. The reaction mixture was heated at 65°C for 18 hrs, the reaction was allowed to cool to room temperature and poured into 2N hydrochloric acid. The mixture was extracted with ethyl acetate and the extract evaporated to give a brown oil. This was passed down a silica gel column eluted with ethyl acetate:hexane (4:1) to afford the product as a yellow solid (0.62g).

| | |
|---|---|
| $^1$H NMR: $CDCl_3$ d: | 4.20 (bs, 2H), 4.77 (m, 2H), |
| | 5.27 (dd, 1H), 5.39 (dd, 1H), 5.89 (bs, 1H), |
| | 6.03 (m, 1H), 6.68 (d, 1H), 7.56 (m, 2H). |

b) Propen-3-yl 2-[2-(4-(3,4-dichlorobenzylthio)phenoxy)-1-hydroxyethyl]benzoxazole-6-carboxylate.

The procedure described in example 1i was used with the product from 21e and the product from 25a to give the required product as a yellow solid in 14% yield.

| | |
|---|---|
| $^1$H NMR: $CDCl_3$ d: | 3.28 (d, 1H), 3.88 (s, 2H) 4.49 (m, 2H), |
| | 4.87 (d, 2H), 5.3-5.47 (m, 3H), 6.06 (m, 1H), |
| | 6.84 (d, 2H), 6.97 (dd,1H), 7.2-7.31 (m, 4H), |
| | 7.78 (d, 1H), 8.14 (dd, 1H), 8.28 (s, 1H). |

**c) Propen-3-yl 2-[2-(4-(3,4-dichlorobenzylthio)phenoxy)-1-oxoethyl]benzoxazole-6-carboxylate.**

The procedure described in example 1j was used with the product from 25b to give the required product as a yellow solid in 56% yield.

$^1$H NMR: $CDCl_3$ d: 3.89 (s, 2H), 4.89 (m, 2H), 5.35 (dd, 1H), 5.45 (dd, 1H), 5.55 (s,2H), 6.07 (m, 1H), 6.92 (d, 2H), 6.98 (dd,1H), 7.23-7.28 (m, 3H), 7.31 (d,1H), 7.97 (m, 2H), 8.41 (s, 1H).

**d) 2-[2-(4-(3,4-Dichlorobenzylthio)phenoxy)-1-oxoethyl]benzoxazole-6-carboxylic acid**

Dry nitrogen was bubbled through dry THF (10 ml) for 0.5hrs. The product from 25c (0.14g) was added followed by tetrakis(triphenylphosphine)palladium (0.02g) and acetic acid (0.3 ml). The reaction was stirred at 25°C, under nitrogen for 2 hrs. The reaction was evaporated and the residue passed down a silica gel column eluted with 5% methanol in dichloromethane to give the product as a pale yellow solid (0.092g).

Mass spectrum: m/e 488 / 490 / 492 (M+1)
M.p.: 179-180°C

## EXAMPLE 26

**2-[2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylic acid**

**a) 2-[4-(3,5-Dichlorobenzyloxy)phenoxy]acetonitrile**

The procedure described in example 1e was used with 2-bromoacetonitrile and 4-(3,5-dichlorobenzyloxy)phenol to give the required product as a yellow oil in 82% yield.

$^1$H NMR: $CDCl_3$ d: 4.72 (s, 2H), 4.98 (s, 2H), 6.94 (m, 4H), 7.32 (s, 3H).

**b) 2-[4-(3,5-Dichlorobenzyloxy)phenoxy]acetaldehyde**

The procedure described in example 1f was used with the product of 26a to give the required product as a yellow oil in 84% yield. The product was used directly in the next step.

**c) 3-[4-(3,5-dichlorobenzyloxy)phenoxy]-2-hydroxypropionitrile**

The procedure described in example 1g was used with the product from 26b to give the required product as a white solid in 78% yield.

M.p.: 89-90°C
$^1$H NMR: $CDCl_3$ d: 3.02 (s, 1H), 4.20 (m, 2H), 4.79 (m, 1H), 4.97 (s, 2H), 6.90 (s, 4H), 7.31 (s, 3H).

**d) 3-[4-(3,5-dichlorobenzyloxy)phenoxy]-2-hydroxy-1-ethoxy-1-iminopropane hydrochloride**

The procedure described in example 1h was used with the product from 26c to give the required product as a white solid in 71% yield. This was used directly in the next step.

$^1$H NMR: $DMSO_{d6}$ d: 1.30 (t,3H), 4.17 (d, 2H), 4.44 (m, 2H), 4.78 (s, 1H), 5.09 (s, 2H), 5.92 (m, 4H), 7.49 (s, 2H), 7.57 (s, 1H).

**e) (1,1-Dimethyl)ethyl 2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-hydroxyethyl]benzoxazole-5-carboxylate**

The procedure described in example 1i was used with the product from 26d and the product from example 1b to give the required product as an orange oil in 93% yield.

Mass spectrum: m/e 530 / 532 / 534 (M+1)
$^1$H NMR: $CDCl_3$ d: 1.62 (s, 9H), 3.31( d, 1H), 4.47 (m, 2H), 4.95 (s, 2H), 5.34 (m, 1H), 6.87 (d, 4H), 7.30 (s, 3H), 7.56 (d, 1H), 8.07 (dd, 1H), 8.39 (d, 1H).

**f) (1,1-Dimethyl)ethyl 2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylate.**

The procedure described for example 1j was used with the product from example 26e to give the product as an off-white solid in 94% yield.

Mass spectrum: m/e 528 / 530 / 532 (M+1)
$^1$H NMR: $CDCl_3$ d: 1.64 (s, 9H), 4.97 (s, 2H), 5.52 (s, 2H), 6.94 (q, 4H), 7.31 (s, 3H), 7.71 (d, 1H), 8.25 (d, 1H),8.56 (d, 1H).

**g) 2-[2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylic acid**

The procedure described in example 1k was used with the product from 26f to give the required product as a white solid in 62% yield.

Mass spectrum: m/e 472 / 474 / 476 (M+1)
M.p.: 169-170°C
$C_{23}H_{15}NCl_2O_6$ requires: C 58.4 H 3.2 N 3.0 %
found: C 57.5 H 3.0 N 3.0 %

**EXAMPLE 27**
**2-[2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl]benzimidazole-5-carboxylic acid**

**a) Propen-3-yl 3,4-diaminobenzoate**

The procedure described for example 25a was used with 3,4-diaminobenzoic acid to afford the product as a brown solid in 43% yield.

$^1$H NMR: $CDCl_3$ d: 4.77 (m, 2H), 5.26 (dd, 1H), 5.35 (dd, 1H), 6.02 (m, 1H), 6.65 (d, 1H), 7.43 (d, 1H), 7.51 (dd, 1H).

**b) Propen-3-yl 2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-hydroxyethyl]-5-benzimidazole carboxylate.**

The procedure described in example 1i was used with the product from 26d and product from 27a to give the required product as a light brown oil in 61% yield.

Mass spectrum: m/e 513 / 515 / 517 (M+1)

**c) Propen-3-yl 2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl]-5-benzimidazole carboxylate.**

The procedure described in example 1j was used with the product from 27b to give the required product as a yellow solid in 78% yield.

Mass spectrum: m/e 511 / 513 / 515 (M+1)

$^1$H NMR: $DMSO_{D6}$ d: 4.85 (d, 2H), 5.08 (s, 2H), 5.31-5.46 (m, 2H), 5.66 (s, 2H) 6.09 (m, 1H), 6.96 (m, 4H), 7.50 (s, 2H), 7.57 (m, 1H), 7.70 (d, 1H), 8.02 (dd, 1H) 8.230 (d, 1H).

**d) 2-[2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl]benzimidazole-6-carboxylic acid**

The procedure used in example 25d was used with the product from 26c to give the product as a pale yellow solid in 38 % yield, as the hydrate.

Mass spectrum: m/e 471 / 473 / 475 (M+1)

M.p.: >300°C

$C_{23}H_{16}N_2Cl_2O_5.H_2O$ requires: C 56.5 H 3.7 N 5.7 %

found: C 56.8 H 3.6 N 5.5 %

**EXAMPLE 28**

**3-[2-(2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl)benzoxazol-5-yl]propionic acid**

**a) Propen-3-yl 3-(3-hydroxy-4-aminophenyl)propionate**

The procedure described for example 25a was used with 3-(3-hydroxy-4-aminophenyl)propionic acid to afford the product as a brown solid in 41% yield.

$^1$H NMR: $CDCl_3$ d: 2.60 (t, 2H), 2.82 (t, 2H), 4.58 (m, 2H), 5.27 (dd, 1H), 5.31 (dd, 1H), 5.90 (m, 1H), 6.5-6.8 (m, 3H).

**b) Propen-3-yl 3-[2-(2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-hydroxyethyl)benzoxazol-5-yl]propionate.**

The procedure described in example 1i was used with the product from 28a and the product from example 27d to give the required product as a light brown solid in 78% yield.

$^1$H NMR: $CDCl_3$ d: 2.70 (t, 2H), 3.08 (t, 2H), 3.30 (d, 1H), 4.43 (m, 2H), 4.58 (m, 2H), 4.95 (s, 2H), 5.20-5.33 (m, 3H), 5.88 (m, 1H), 6.87 (m, 4H), 7.21 (dd, 1H), 7.30 (s, 3H), 7.45 (d, 1H), 7.56 (d, 1H).

**c) Propen-3-yl 3-[2-(2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl)benzoxazol-5-yl]propionate.**

The procedure described for example 1j was used with the product from example 28b to give the product as an yellow solid in 94% yield.

Mass spectrum: m/e 540 / 542 / 544 (M+1)

$^1$H NMR: $CDCl_3$ d: 2.74 (t, 2H), 3.14 (t, 2H), 4.58 (m, 2H), 4.97 (s, 2H), 5.21-5.26 (m, 2H), 5.50 (s, 2H), 5.88 (m, 1H), 6.88-6.99 (q, 4H), 7.26 (s, 2H), 7.31 (s, 1H), 7.42 (dd, 1H), 7.61 (d, 1H), 7.73 (s, 1H).

**d) 2-[2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl]benzoxazole-5-yl]propionic acid**

The procedure described in example 25d was used with the product from 28c to give the required product as an off-white solid in 47% yield.

Mass spectrum: m/e 500 / 502 / 504 (M+1)

M.p.: 134-135°C

$C_{25}H_{19}Cl_2NO_6$ requires: C 60.0 H 3.8 N 2.8 %

found: C 59.8 H 3.8 N 3.0 %

## EXAMPLE 29

## 2-[3-[4-(Phenylpentyloxy)phenyl]-1-oxopropyl]benzoxazole-5- carboxylic acid

### a) Methyl 3-(4-(5-phenylpentyloxy)phenyl)propionate

A solution of methyl 3-(4-hydroxyphenyl)propionate (4.6g) in dry DMF (100 ml) was treated with sodium hydride (60% oil suspension, 1.02g) and stirred at 25°C, under an atmosphere of nitrogen for 10 mins. A solution of phenylpentyl mesylate (6.18g) in DMF (20 ml) was added dropwise and stirring was continued for 18 hrs. The reaction mixture was poured into 2N hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, brine, dried ($MgSO_4$), evaporated and the resulting oil passed down a silica gel column eluted with hexane:ethyl acetate (20:1, v/v) to give the product as a white solid (5.85g).

Mass spectrum: m/e 326

$^1H$ NMR: $CDCl_3$ d: 1.45-1.85 (m, 6H), 2.61 (m, 4H), 2.88 (t, 2H), 3.66 (s,3H), 3.92 (t, 2H), 6.81-7.10 (m, 4H), 7.27-7.9 (m, 5H).

### b) 3-(4-(5-Phenylpentyloxy)phenyl)propionic acid

The procedure described in example 9b was used with the product of 29a to give the product as a white solid in 94% yield.

Mass spectrum: m/e 312

$^1H$ NMR: $CDCl_3$ d: 1.50 (m, 2H), 1.68 (m, 2H), 1.80 (m, 2H), 2.64 (m,4H), 2.90 (t, 2H), 3.92 (t, 2H), 6.82 (d, 2H), 7.11 (d, 2H), 7.1-7.3 (m, 5H).

### c) N-Methyl,N-methoxy-3-[4-(5-phenylpentyloxy)phenyl]propionamide

The product of 29b (5.2g) was dissolved in thionyl chloride (50 ml) and heated at reflux for 4 hrs. The mixture was evaporated and then co-evaporated with toluene (50 ml), the residue was dissolved in dry dichloromethane (100 ml) and the solution was cooled to 0°C under a nitrogen atmosphere. N,O-dimethylhydroxyamine (1.78g) was added followed by the dropwise addition of pyridine (2.96 ml). The reaction was stirred at 25°C for 3 hrs then

washed with 2N hydrochloric acid, saturated sodium bicarbonate solution, brine, dried ($MgSO_4$) and evaporated to give an orange oil. The oil was passed down a silica gel column eluted with hexane:ethyl acetate (2:1, v/v) to give the product as a colourless oil, (4.14g).

Mass spectrum: m/e 355

$^1$H NMR: $CDCl_3$ d: 1.50 (m, 2H), 1.71 (m, 2H), 1.80 (m, 2H), 2.64 (t, 2H), 2.70 (m, 2H), 2.88 (m, 2H), 3.17 (s, 3H), 3.60 (s, 3H), 3.94 (t, 2H), 6.81 (d, 2H), 7.15 (d, 2H), 7.15-7.3 (m, 5H).

**d) 3-[4-(5-Phenylpentyloxy)phenyl]propionaldehyde**

The amide product of 29c (4.1g) was dissolved in dry THF (30 ml), cooled to 0°C and stirred under a nitrogen atmosphere. A 1M solution of lithium aluminium hydride in THF (7 ml) was added dropwise and stirring continued for 0.5 hr. A solution of sodium hydrogenphosphate (4g) in water (80 ml) was added and the mixture was extracted with ether. The extract was washed with water, brine, dried ($MgSO_4$) and evaporated to give the product as a yellow oil (3.4g).

Mass spectrum: m/e 296

$^1$H NMR: $CDCl_3$ d: 1.51 (m, 2H), 1.71 (m, 2H), 1.82 (m, 2H), 2.65 (m, 2H), 2.76 (t, 2H), 2.91 (t, 2H), 3.92 (t, 2H), 6.82 (d, 2H), 7.10 (d, 2H), 7.15-7.85 (m, 5H), 9.81 (s, 1H).

**e) 4-[4-(5-Phenylpentyloxy)phenyl]-2-hydroxy-butyronitrile**

The procedure described in example 1g was used with the product from 29d to give the product as a white solid in 68% yield.

Mass spectrum: m/e 324

$^1$H NMR: $CDCl_3$ d: 1.51 (m, 2H), 1.67 (m, 2H), 1.80 (m, 2H), 2.12 (m, 2H), 2.59 (d,1H), 2.62 (t, 2H), 2.79 (t, 2H), 3.93 (t, 2H), 4.41 (m, 1H), 6.82 (d, 2H), 7.10 (d, 2H), 7.15-7.30 (m, 5H).

f) 4-[4-(5-Phenylpentyloxy)phenyl]-2-hydroxy-1-ethoxy-1-iminobutane hydrochloride

The procedure described in example 1h was used with the product from 29e to give the product as a white solid in 80% yield.

Mass spectrum: m/e 370 (M+1)
$^1$H NMR: DMSO-$D_6$ d: 1.32 (t, 3H), 1.43 (m, 2H), 1.63 (m, 2H), 1.72 (m, 2H), 1.90 (m, 2H), 2.60 (m, 4H), 3.91 (t, 2H), 4.36 (m, 1H), 4.39 (m, 2H), 6.78 (s, 1H), 6.83 (d, 2H),7.10 (d, 2H). 7.15-7.32 (m, 5H), 11.17 (bs, 2H).

g) 2-[3-(4-(5-Phenylpentyloxy)phenyl)-1-hydroxypropyl] benzoxazole-5-carboxylic acid

The procedure described in example 1i was used with the product from 29f to give the product as a white solid in 51% yield.

Mass spectrum: m/e 460 (M+1)
M.p.: 136-137°C

| | | |
|---|---|---|
| $C_{28}H_{29}NO_5$ | requires: | C 73.2 H 6.4 N 3.1 % |
| | found: | C 73.1 H 6.5 N 3.1 % |

h) 2-[3-(4-(5-Phenylpentyloxy)phenyl)-1-oxopropyl]benzoxazole-5- carboxylic acid

The procedure described in example 1j was used with the product from 29g to give the product as a white solid in 74% yield which analysed as the hemihydrate.

Mass spectrum: m/e 458 (M+1)
M.p.: 141-142°C

| | | |
|---|---|---|
| $C_{28}H_{27}NO_5 0.5H_2O$ | requires: | C 72.1 H 6.1 N 3.0 % |
| | found: | C 72.6 H 6.0 N 3.4 % |

**EXAMPLE 30**

**2-[3-(4-(5-Phenylpentyloxy)phenyl)-1-oxopropyl]benzoxazole-6- carboxylic acid**

**a) 2-[3-(4-(5-Phenylpentyloxy)phenyl)-1-hydroxypropyl] benzoxazole-6-carboxylic acid**

The procedure described in example 1i was used with the product from 29f and 3-hydroxy-4-aminobenzoic acid to give the product as a white solid in 45% yield.

Mass spectrum: m/e 460 (M+1)
M.p.: 123-124°C

| | | |
|---|---|---|
| $C_{28}H_{29}NO_5$ | requires: | C 73.2 H 6.4 N 3.1 % |
| | found: | C 73.0 H 6.5 N 3.2 % |

**b) 2-[3-(4-(5-Phenylpentyloxy)phenyl)-1-oxopropyl]benzoxazole-5- carboxylic acid**

The procedure described in example 1j was used with the product from 30a to give the product as a white solid in 53% yield.

Mass spectrum: m/e 457
M.p.: 152-153°C

| | | |
|---|---|---|
| $C_{28}H_{27}NO_5$ | requires: | C 73.5 H 6.0 N 3.1 % |
| | found: | C 72.5 H 6.1 N 3.3 % |

**EXAMPLE 31**

**3-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]propionic acid**

5-Oxo-hexanoic acid was subjected to the sequence of reactions described in example 10 to give the title compound as a white solid as the monohydrate.

Mass spectrum: m/e 484 (M+1)
M.p.: 99-101°C

| | | |
|---|---|---|
| $C_{26}H_{29}NO_4S_2$ | requires: | C 62.3 H 6.2 N 2.8 S 12.8 % |
| | found: | C 61.5 H 5.7 N 3.0 S 12.6 % |

**EXAMPLE 32**

**4-[2-(2-(4-(Decylthio)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid**

**a) Ethyl 2-[4-(decylthio)phenoxy)] acetate**

The procedure described for example 2a was used with 4-(decylthio)phenol and ethyl 2-bromoacetate to give the required compound as a yellow solid in 95% yield.

Mass spectrum: m/e 353 (M+1)

$^1$H NMR: $CDCl_3$ d: 0.88 (t, 3H), 1.2-1.35 (m, 15H), 1.4 (m, 2H), 1.6 (m, 2H), 2.82 (t, 2H), 4.29 (q, 2H), 4.6 (s, 2H), 6.86 (d, 2H), 7.33 (d, 2H).

**b) 4-[2-(2-(4-(Decylthio)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoicacid**

The procedure described in example 10e was used with the product of 32a and the product from 10d to afford the product as a yellow solid in 25% yield.

Mass spectrum: m/e 492 (M+1)

$^1$H NMR: $CDCl_3$ d: 0.88 (t, 3H), 1.2-1.3 (m, 12H), 1.4 (m, 2H), 1.61 (m, 2H), 2.0 (m, 2H), 2.44 (s, 3H), 2.46 (t, 2H), 2.8 (t, 2H), 2.9 (t, 2H), 5.45 (s, 2H) 6.92 (d, 2H), 7.32 (d, 2H).

**EXAMPLE 33**

**4-[2-(2-(4-(Decylsulfonyl)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid**

The procedure described in example 13b was used with the product from example 32b to afford the required product as a yellow solid in 33% yield. This was converted to the dicyclohexylamine salt and analysed as the monohydrate.

Mass spectrum: m/e 524 (M+1)

M.p.: 139°C

| | | |
|---|---|---|
| $C_{38}H_{60}N_2O_6S_2 \cdot H_2O$ | requires: | C 63.1 H 8.6 N 3.9 S 8.9 % |
| | found: | C 63.5 H 8.4 N 4.0 S 8.8 % |

**EXAMPLE 34**

**2-[2-(2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl)benzothiazol-6-oxy]acetic acid**

**a) (1,1-Dimethyl)ethyl 2-(benzothiazol-6-oxy)acetate**

Using the procedure described in example 5a with 6-hydroxybenzothiazole and (1,1-dimethyl)ethyl 2-bromoacetate gave the required product as a yellow oil in 97% yield.

Mass spectrum: m/e 266 (M+1)
$^1$H NMR, $CDCl_3$ , d: 1.49 (s, 9H), 4.60 (s, 2H), 7.17 (dd, 1H)), 7.39 (d, 1H), 8.04 (d, 1H), 8.86 (s, 1H).

**b) 2-(Benzothiazol-6-oxy)acetic acid**

The procedure described in example 5b was used with the product from 34a to give the required product as an off-white solid in quantitative yield.

Mass spectrum: m/e 210 (M+1)
$^1$H NMR, $CDCl_3$ , d: 4.77 (s, 2H), 7.16 (dd, 1H)), 7.70 (d, 1H), 7.98 (d, 1H), 8.35 (s, 1H), 9.20(s, 1H).

**c) 2-[2-(2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl)benzothiazol-6-oxy]acetic acid**

The procedure described in example 8 was used with the product from 34b and the product from 11b to give the required product as a yellow solid in 22% yield.

Mass spectrum: m/e 518 / 520 / 522 (M+1)
M.p.: 179-180°C

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_{24}H_{17}Cl_2NO_6S$ | requires: | C 55.6 | H 3.3 | N 2.7 | S 6.2 % |
| | found: | C 55.6 | H 3.3 | N 2.5 | S 5.9 % |

**EXAMPLE 35**

**4-[2-(2-(4-(5-Phenylpentyloxy)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid**

**a) 5-Phenylpentyl tosylate**

5-Phenylpentanol (12.7g) was dissolved in chloroform (200 ml) and the solution cooled to 0°C. Pyridine (6.9 ml) was added followed by portionwise addition of tosyl chloride (16.2g). The reaction mixture was stirred at ambient temperature for 16 hrs then washed with water, dried ($MgSO_4$) and evaporated to leave a colourless oil. The oil was passed down a silica gel column eluted with hexane:ethyl acetate (4:1) to afford the product as a colourless oil (17.7g).

$^1$H NMR, $CDCl_3$ , d: 1.32-1.4 (m, 2H), 1.5-1.59 (m, 2H), 1.6-1.69 (m, 2H) 2.44 (s, 3H), 2.56 (t, 2H), 4.01 (t, 2H), 7.1-7.2 (m, 3H) 7.24-7.29 (m, 2H), 7.35 (d, 2H), 7.75 (d, 2H).

**b) 4-(5-Phenylpentyloxy)phenol**

Quinol (8.3g) was dissolved in acetonitrile (200 ml) and treated with caesium carbonate (24.5g) and the tosylate from 35a (8.0g). The mixture was heated at 85oC for 24 hrs. The mixture was cooled to ambient temperature, poured into 2N hydrochloric acid (200 ml) and extracted into ethyl acetate. The extract was washed with water, brine, dried (MgSO4) and evaporated to give a solid. The solid was passed down a silica gel column eluted with hexane:ethyl acetate (4:1) to afford the product as a white solid (3.0g).

Mass spectrum: m/e 256

$^1$H NMR, $CDCl_3$ , d: 1.47-1.53 (m, 2H), 1.65-1.7 (m, 2H), 1.75-1.8 (m, 2H) 2.64 (t, 2H), 3.9 (t, 2H), 4.4 (s, 1H), 6.74-6.8 (dd, 4H) 7.16-7.2 (m, 3H), 7.26-7.3 (m, 2H).

**c) Ethyl 2-[4-(5-phenylpentyloxy)phenoxy]acetate.**

The procedure described in example 2a was used with the product from 35b to give the required product as a yellow solid in 90% yield.

Mass spectrum: m/e 342

$^1$H NMR, $CDCl_3$ , d: 1.29 (t, 3H), 1.47-1.52 (m, 2H), 1.65-1.71 (m, 2H), 1.74-1.79 (m, 2H)
2.64 (t, 2H), 3.89 (t, 2H), 4.26 (q, 2H), 4.56 (s, 2H)
6.8-6.86 (dd, 4H), 7.18 (m, 3H), 7.26-7.29 (m, 2H).

**d) 4-[2-(2-(4-(5-Phenylpentyloxy)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid**

The procedure described in example 8 was used with the product from 35c and the product from 10d to give the required product as a yellow solid in 20% yield.

Mass spectrum: m/e 482 (M+1)

M.p.: °C 127-128

| | | | | | |
|---|---|---|---|---|---|
| $C_{27}H_{31}NO_5S$ | requires: | C 67.3 | H 6.5 | N 2.9 | S 6.7 % |
| | found: | C 66.8 | H 6.4 | N 2.9 | S 6.4 % |

**EXAMPLE 36**

**5-[2-(2-(4-(5-Phenylpentyloxy)phenoxy)-1-oxoethyl)thiazol-4-yl]pentanoic acid**

**a) Methyl 7-bromo-6-oxo-heptanoate**

To a solution of 6-oxoheptanoic acid (6.06g) in methanol (100 ml) was added dropwise a solution of bromine (7.2g) in ~~meth~~anol (20 ml). The mixture was then stirred at 25°C for 18 hrs. The solvent was removed under reduced pressure and the residue was dissolved in ethyl acetate (250 ml). This was washed with a saturated solution of sodium bicarbonate, water, brine, dried ($MgSO_4$) and evaporated to a gum which was passed down a silica gel column eluted with hexane:ether (3:1, v/v). The appropriate fractions were combined and evaporated to give the product as a pale yellow oil, (3.05g).

Mass spectrum: m/e 236 / 238 (M+)

$^1$H NMR, $CDCl_3$ , d: 1.6-1.7 (m, 4H), 2.3-2.4 (m, 2H)),
2.66-2.72 (m, 2H), 3.67 (s, 3H), 3.88 (s, 2H).

**b) Methyl 5-(thiazol-4-yl)pentanoate**

Formamide (10 ml) in toluene (30 ml) was treated with phosphorus pentasulphide (3.5g). Methyl 7-bromo-6-oxoheptanoate (2.6g) was added and the mixture was heated at 75 °C for 2 hrs. The reaction mixture was allowed to cool to ambient temperature, neutralised with 10% sodium hydroxide solution and extracted with ethyl acetate. The extract was washed with water, brine, dried ($MgSO_4$) and evaporated to give a gum. This was passed down a silica gel column eluted with hexane:ethyl acetate (3:2, v/v) to afford the product as a colourless oil (1.37g).

| | |
|---|---|
| Mass spectrum: m/e | 200 (M+1) |
| $^1$H NMR, $CDCl_3$ , d: | 1.6-1.8 (m, 4H), 2.36 (t, 2H)), 2.86 (t, 2H), 3.67 (s, 3H), 6.96 (d, 1H), 8.74(d, 1H). |

**c) 5-(Thiazol-4-yl)pentanoic acid**

The procedure described in example 10d was used with the product from 36a to give the required product as a yellow solid in 94% yield.

| | |
|---|---|
| Mass spectrum: m/e | 186 (M+1) |
| $^1$H NMR, $CDCl_3$ , d: | 1.7-1.9 (m, 4H), 2.40 (t, 2H)), 2.87 (t, 2H), 6.97 (d, 1H), 8.79(d, 1H). |

**d) 5-[2-(2-(4-(5-Phenylpentyloxy)phenoxy)-1-oxoethyl)thiazol-4-yl]pentanoic acid**

The procedure described in example 8 was used with the product from 36b and the product from 35b to give the required product as a yellow solid in 24% yield.

Mass spectrum: m/e 482 (M+1)

M.p.: 78-80°C

| | | |
|---|---|---|
| $C_{27}H_{31}NO_5S$ | requires: | C 67.3 H 6.5 N 2.9 S 6.7 % |
| | found: | C 67.8 H 6.5 N 2.9 S 6.1 % |

**EXAMPLE 37**

**4-[2-(2-(4-(5-Phenylpentyloxy)phenyl)-1-oxopropyl) -4-methylthiazol-5-yl]butanoic acid**

a) Methyl 4-(4-methylthiazol-5-yl)butanoate

Using the procedure described in 36b, with methyl 5-bromo-6-oxo-heptanoate led to the required product as a yellow solid in 74% yield.

$^1$H NMR, $CDCl_3$, d: 1.95 (m, 2H), 2.36 (t, 2H), 2.38 (s, 3H), 2.82 (t, 2H), 3.68 (s, 3H), 8.56 (s, 1H).

b) 4-(4-methylthiazol-5-yl)butanoic acid

Using the procedure described in 9b, with the product from 37a, led to the required product as a white solid in 63% yield.

Mass spectrum : m/e 186 (M+1)
$^1$H NMR, $DMSO_{d6}$, d: 1.76 (m, 2H), 2.26 (t, 2H), 2.29 (s, 3H), 2.77 (t, 2H), 8.81 (s, 1H), 12.11 (s, 1H).

c) 4-[2-(2-(4-(5-Phenylpentyloxy)phenyl)-1-oxopropyl) -4-methylthiazol-5-yl]butanoic acid

The procedure described in example 8 was used with the product from 37b and the product from 29a to give the required product as a yellow solid in 10% yield.

Mass spectrum: m/e 480
M.p.: 121-122°C

**EXAMPLE 38**

**4-[2-(2-(4-(Benzylthio)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid**

The procedure described in example 8 was used with the product from 37b and the product from 15b to give the required product as a white solid in 25% yield.

Mass spectrum: m/e 442 (M+H)
M.p.: °C 131-132

| | | |
|---|---|---|
| $C_{23}H_{23}NO_4S_2$ | requires: | C 62.6 H 5.3 N 3.2 S 14.5 % |
| | found: | C 61.8 H 5.1 N 3.3 S 14.0 % |

**EXAMPLE 39**

**2-[2-(4-(3,5-Dichlorobenzyloxy)phenoxy)-1-oxoethyl]benzothiazole-6- carboxylic acid**

The procedure described in example 8 was used with the product from 11b to give the required product as a white solid in 20% yield.

Mass spectrum: m/e 486 / 488 / 490 (M+H)
M.p.: °C 205-205

| | | |
|---|---|---|
| $C_{23}H_{15}Cl_2NO_5S$ | requires: | C 56.6 H 3.1 N 2.9 S 6.6 % |
| | found: | C 55.4 H 3.1 N 3.0 S 6.6 % |

**EXAMPLE 40**

**4-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-1-oxopropyl)-4-methylthiazol-5-yl]butanoic acid**

**a) Ethyl 2-[4-(5-phenylpentylthio)phenoxy]propionate**

The procedure described in example 2a was used starting with ethyl 2-bromopropionate to give the product as a colourless oil in 87% yield.

Mass spectrum: m/e 373 (M+H)

| | |
|---|---|
| $^1$H NMR, $CDCl_3$ , d: | 1.24 (t, 3H), 1.41 (m, 2H), 1.51-1.65 (m & d, 7H), 2.59 (t, 2H), 2.80 (t, 2H), 4.21 (q, 2H), 4.70 (q, 1H), 6.80 (d, 2H), 7.14-7.21 (m, 3H), 7.24-7.31(m, 4H). |

b) 4-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-1-oxopropyl)-4-methylthiazol-5-yl]butanoic acid

The procedure described in example 10e was used with the product from 40a to give the required product as a pale yellow gum in 43% yield. The product was converted to the dicyclohexylamine salt which was a pale yellow solid.

Mass spectrum: m/e 512 (M+H)
M.p.: °C 107-108

| | | | |
|---|---|---|---|
| $C_{40}H_{56}N_2O_4S_2$ | requires: | C 69.3 | H 8.2 N 4.0 S 9.3 % |
| | found: | C 69.6 | H 8.2 N 4.3 S 9.3 % |

EXAMPLE 41

4-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-1-oxo-2-methyl-propyl)-4-methylthiazol-5-yl]butanoic acid

a) Ethyl 2-[4-(5-phenylpentylthio)phenoxy]2-methylpropionate

The procedure described in example 40a was used starting with ethyl 2-bromo-2-methylpropionate to give the product as a colourless oil in 45% yield.

b) 4-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-1-oxo-2-methylpropyl)-4-methylthiazol-5-yl]butanoic acid

The procedure described in example 10e was used with the product from 41a to give the required product as a pale yellow gum in 22% yield.

Mass spectrum: m/e 526 (M+H)
$^1$H NMR, $CDCl_3$ , d: 1.42 (m, 2H), 1.61 (m, 4H), 1.76 (s, 6H), 1.95 (m, 2H), 2.44 (s & m, 5H), 2.60 (t, 2H), 2.83 (m, 4H), 6.77 (d, 2H), 7.13-7.29 (m, 7H).

**EXAMPLE 42**

**4-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-2-phenyl-1-oxyethyl)-4-methylthiazol-5-yl]butanoic acid**

**a) Methyl 2-[4-(5-phenylpentylthio)phenoxy]2-phenylacetate**

The procedure described in example 40a was used starting with methyl 2-bromo-2-phenylacetate to give the product as a white solid in 75% yield.

Mass spectrum: m/e 421 (M+H)

$^1$H NMR, $CDCl_3$ , d: 1.44 (m, 2H), 1.61 (m, 4H), 2.58 (t, 2H), 2.81 (t, 2H), 3.74 (s,3H), 5.60 (s, 1H), 6.85(d, 2H), 7.15 (m, 3H), 7.25 (m, 4H), 7.41 (m,3H), 7.55 (m,2H).

**b) 4-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-1-oxo-2-phenylethyl)-4-methylthiazol-5-yl]butanoic acid**

The procedure described in example 10e was used with the product from 42a to give the required product as a pale yellow gum in 8% yield. This was converted to the dicyclohexyllamine salt to afford a white solid, which analysed as the hydrate.

Mass spectrum: m/e 574 (M+H)

M.p.: °C 121-122

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_{45}H_{58}N_2O_4S_2$ | $.H_2O$ | requires: | C 69.9 | H 7.8 | N 3.6 | S 8.3 % |
| | | found: | C 70.0 | H 7.4 | N 3.5 | S 7.8 % |

**EXAMPLE 43**

**4-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-3-methyl-1-oxobutyl)-4-methylthiazol-5-yl]butanoic acid**

**a) Ethyl 2-[4-(5-phenylpentylthio)phenoxy]3-methylbutanoate**

The procedure described in example 40a was used starting with ethyl 2-bromo-3-methylbutanoate to give the product as a clear oil in 35% yield.

Mass spectrum: m/e 401 (M+H)

$^1$H NMR, $CDCl_3$ , d: 1.05-1.09 (2xt, 6H), 1.24 (t,3H), 1.43 (m, 2H), 1.60 (m, 4H), 2.27 (m, 1H), 2.59 (t,2H), 2.80 (t, 2H), 4.21 (q, 2H), 4.32 (d, 1H), 6.82 (d, 2H), 7.17 (m, 3H), 7.24-7.30 (m, 4H).

**b) 4-[2-(2-(4-(5-Phenylpentylthio)phenoxy)-3-methyl-1-oxobutyl)-4-methylthiazol-5-yl]butanoic acid**

The procedure described in example 10e was used with the product from 42a to give the required product as a pale yellow gum in 11% yield. This was converted to the dicyclohexyllamine salt to afford a white solid.

Mass spectrum: m/e 540 (M+H)
M.p.: °C 111-112

| | | |
|---|---|---|
| $C_{42}H_{60}N_2O_4S_2$ | requires: | C 69.9 H 8.4 N 3.9 S 8.9 % |
| | found: | C 69.8 H 8.5 N 3.9 S 9.2 % |

**EXAMPLE 44**

**2-[2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl]benzimidazole-5-carboxylic acid**

**a) 2-[2-(4-(5-Phenylpentylthio)phenoxy)-1-hydroxyethyl]benzimidazole-5-carboxylic acid**

The procedure described in example 1i was used with 3,4-diaminobenzoic acid to afford the required product as a light brown solid in 70% yield.

Mass spectrum: m/e 478 (M+H)
$^1$H NMR, $CDCl_3$, d: 1.36 (m, 2H), 1.53 (m, 4H), 2.53 (t, 2H), 2.82 (t, 2H), 4.26-4.45 (m, 2H) 5.20 (m, 1H), 6.37 (d,1H) 6.94 (d, 2H), 7.12-7.29 (m, 7H), 7.58 (dd, 1H), 7.80 (m, 1H), 8.12 (d, 1H).

**b) 2-[2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl]benzimidazole-5-carboxylic acid**

The procedure described in example 1i was used with the product from 44a to afford the required product as a cream coloured solid in 32% yield, as the hemi-hydrate.

Mass spectrum: m/e 475 (M+H)

M.p.: °C 186-188

| | | |
|---|---|---|
| $C_{27}H_{26}N_2O_4S.0.5H_2O$ | requires: | C 67.1 H 5.6 N 5.8 S 6.6 % |
| | found: | C 67.7 H 5.6 N 5.9 S 6.7 % |

**EXAMPLE 45**

**2-[2-[4-(5-Phenylpentylthio)phenoxy]-1-oxoethyl]imidazole**

**a) 1-Triphenylmethyl-2-[2-[4-(5-Phenylpentylthio)phenoxy]-1-oxoethyl]imidazole**

The procedure described in example 2b was used with 1-triphenylmethylimidazole to afford the required product as a colourless oil in 37% yield.

$^1$H NMR, $CDCl_3$, d: 1.44 (m, 2H), 1.60 (m, 4H), 2.59 (t, 2H), 2.76 (t, 2H), 5.18 (s, 2H), 6.33 (d,2H) 7.06 (m, 6H), 7.12-7.19 (m, 7H), 7.25-7.28 (m, 11H).

**b) 2-[2-[4-(5-Phenylpentylthio)phenoxy]-1-oxoethyl]imidazole**

The product from example 45a (0.64g) was dissolved in dichloromethane (50 mls) and treated with trifluoroacetic acid (8 mls) and stirred at 25°C for 0.5 hr. The reaction mixture was then poured into a 5% solution of sodium hydroxide in water (200 mls) and extracted with dichloromethane. The extract was dried (MgSO4) and evaporated to dryness. The residue was passed down a silica gel columned eluted with hexane:ethyl acetate (2:1) to afford the required product as a white solid (0.32g).

Mass spectrum: m/e 381 (M+H)

M.p.: °C 162-163

| | | |
|---|---|---|
| $C_{22}H_{24}N_2O_4S$ | requires: | C 69.4 H 6.4 N 7.4 S 8.4 % |
| | found: | C 69.6 H 6.5 N 7.0 S 8.2 % |

**EXAMPLE 46**

**3-[2-[2-[4-(5-Phenylpentylthio)phenoxy]-1-oxoethyl]-4-methylimidazol-5-yl]propenoic acid**

**a) (1-Triphenylmethyl-4-methylimidazol-5-yl)carboxaldehyde**

4-Methyl-imidazole-5-carboxaldehyde (2.0 g) was dissolved in DMF (40 mls) and treated with triethylamine (1.84 g). Triphenylmethylchloride (5.06g) in DMF (40 mls) was added over 0.5 hr and the reaction was stirred at ambient temperature for 18 hrs. The reaction mixture was poured into water and extracted into ethyl acetate. The extract was washed with water, brine, dried (MgSO4) and evaporated to afford an oil. This was passed down a silica gel column eluted with hexane:ethyl acetate (1:1) to give the product as a white solid (2.39 g).

H NMR, $CDCl_3$, d: 1.6 (s, 1H), 7.10-7.19 (m, 6H), 7.34-7.38 (m, 9H),7.39(s,1H), 10.00 (s, 1H).

**b) Ethyl 3-(1-Triphenylmethyl-4-methylimidazol-5-yl)propenoate**

The product from example 46a (2.39 g) was dissolved in dichloromethane (50 mls) and treated with (carbethoxymethylene)phosphorane (2.36 g) and stirred at ambient temperature for 24 hrs. The reaction was then stirred at reflux for 72 hrs. The solvent was removed under reduced pressure and the residue purified by silica gel chromatography, eluted with hexane:ethyl acetate (3:2), to give the required product as a white solid (1.45g).

H NMR, $CDCl_3$, d: 1.29 (t, 3H), 1.57 (s, 3H), 4.22 (q, 2H), 6.58 (d, 1H), 7.12-7.17 (m, 6H), 7.26-7.36 (m, 10H), 7.55 (d,1H).

**c) 3-(1-Triphenylmethyl-4-methylimidazol-5-yl)propenoic acid**

The product from example 46b (1.45 g) was dissolved in tetrahydrofuran (40 mls) and water (10 mls) was added. Lithium hydroxide monohydrate (0.43g) was added followed by a few drops of methanol and the mixture stirred at room temperature for 18 hrs. The mixture was then heated at reflux for 6 hrs, then poured into a saturated solution of ammonium chloride (30 mls) and extracted into ethyl acetate. The extracts were washed with water, brine, dried (MgSO4) and evaporated to dryness to give the product as a white solid (1.27 g).

H NMR, $CDCl_3$, d: 1.57 (s, 3H), 6.60 (d, 1H), 7.11-7.19 (m, 6H), 7.32-7.36 (m, 9H), 7.41 (s, 1H), 7.62 (d, 1H).

**d) 3-[2-[2-[4-(5-Phenylpentylthio)phenoxy]-1-oxoethyl]-1-triphenylmethyl-4-methylimidazol-5-yl]propenoic acid**

The procedure described in example 8 was used with the product from example 46c to give the required product in 21% yield.

$^1$H NMR, $CDCl_3$, d: 1.44 (m, 2H), 1.59 (m, 4H), 1.74 (s, 3H), 2.59 (m, 2H) 2.79 (t, 2H), 5.11 (s, 2H), 6.85 (d,1H), 6.75 (d,2H) 7.1-7.19 (m, 9H), 7.24-7.39 (m, 13H), 7.62 (d,1H).

**e) 3-[2-[2-[4-(5-Phenylpentylthio)phenoxy]-1-oxoethyl]-4-methylimidazol-5-yl]propenoic acid**

The procedure described in example 45b was used with the product from example 46d to afford the required product in 10% yield.

Mass spectrum: m/e 465 (M+H)

$^1$H NMR, $CDCl_3$, d: 1.44 (m, 2H), 1.61 (m, 4H), 2.40 (s, 3H), 2.60 (t, 2H) 2.81 (t, 2H), 5.45 (s, 2H), 6.60 (d,1H), 6.93 (d,2H) 7.14 (m, 3H), 7.16-7.32 (m, 4H), 7.61 (d,1H), 13.1 (bs, 1H).

**EXAMPLE 47**

**2-[2-(4-(5-Phenylpentylthio)phenoxy)-1-oxoethyl]pyridine**

Using the procedure described for example 5d but using 2-bromopyridine in place of 1-methylimidazole led to the preparation of the required compound as a white solid in 57% yield.

Mass spectrum: m/e 392 (M+H)

M.p.: 68°C

$C_{24}H_{25}NO_2S$ requires: C 73.6 H 6.4 N 3.6 S 8.2 %

found: C 74.6 H 6.5 N 3.7 S 8.1 %

**EXAMPLE 48**

**4-[2-(2-(4-(5-Phenylpentyloxy)phenoxy)-1-oxopropyl)-4-methylthiazol-5-yl]butanoic acid**

a) Ethyl 2-[4-(5-phenylpentyloxy)phenoxy]propionate

The procedure described in example 2a was used starting with ethyl 2-bromopropionate and (5-phenylpentyloxy)phenol to give the product as a colourless gum.

Mass spectrum: m/e 366 (M+H)
$^1$H NMR, $CDCl_3$ , d: 1.27 (t, 3H), 1.49 (m, 2H), 1.56-1.83 (m & d, 7H), 2.64 (t, 2H), 3.89 (t, 2H), 4.16 (q, 2H), 4.64 (q, 1H), 6.77-6.84 (m, 4H), 7.15-7.30 (m, 5H).

b) 4-[2-(2-(4-(5-Phenylpentyoxy)phenoxy)-1-oxopropyl)-4-methylthiazol-5-yl]butanoic acid

The procedure described in example 10e was used with the product from 48a to give the required product as a pale yellow gum. The product was converted to the dicyclohexylamine salt which was a pale yellow solid.

Mass spectrum: m/e 496 (M+H)
M.p.: °C 91-93

| | | |
|---|---|---|
| $C_{40}H_{56}N_2O_5S$ | requires: | C 70.9 H 8.3 N 4.1 S 4.7 % |
| | found: | C 70.7 H 8.2 N 4.1 S 4.9 % |

EXAMPLE 49

4-[2-(2-(4-(4-Chlorobenzylthio)phenoxy)-1-oxopropyl)-4-methylthiazol-5-yl]butanoic acid

a) 4-(4-Chlorobenzylthio)phenol

The procedure described in example 13a was used with 4-hydroxythiophenol and 4-chlorobenzyl chloride to give the required product as a pale yellow solid in 59% yield.

$^1$H NMR, $CDCl_3$, d: 3.91 (s, 2H), 4.94 (s, 1H), 6.70 (d, 2H), 7.1 (d, 2H) 7.21 (dd, 4H).

b) Ethyl 2-[4-(4-chlorobenzylthio)phenoxy]propionate

The procedure described in example 2a was used with ethyl 2-bromopropionate and 4-(4-chlorobenzylthio)phenol to give the required product as a white solid in 93% yield.

$^1$H NMR, $CDCl_3$, d: 1.26 (t, 3H), 1.60 (d, 3H), 3.92 (s, 2H), 4.20 (q, 2H), 4.71 (q, 1H), 6.77 (d, 2H), 7.1 (d, 2H), 7.22 (m, 4H).

**c) 4-[2-(2-(4-(4-Chlorobenzylthio)phenoxy)-1-oxopropyl)-4-methylthiazol-5-yl]butanoic acid**

The procedure described in example 10e was used with the product from 49b to give the required product as a pale yellow gum. The product was converted to the dicyclohexylamine salt which was a pale yellow solid.

Mass spectrum: m/e 490 / 492 (M+H)
M.p.: °C 106-107

| | | | | | | |
|---|---|---|---|---|---|---|
| $C_{36}H_{47}ClN_2O_4S_2$ | requires: | C 64.4 | H 7.1 | N 4.2 | S 9.6 % |
| | found: | C 63.7 | H 7.1 | N 4.1 | S 9.3 % |

**EXAMPLE 50**

**4-[2-(2-(4-(4-Chlorobenzylthio)phenoxy)-1-oxobutyl)-4-methylthiazol-5-yl]butanoic acid**

**a) Ethyl 2-[4-(4-chlorobenzylthio)phenoxy]butanoate**

The procedure described in example 2a was used with ethyl 2-bromobutanoate and 4-(4-chlorobenzylthio)phenol to give the required product as a white solid in 94% yield.

$^1$H NMR, $CDCl_3$, d: 1.07 (t, 3H), 1.25 (t, 3H), 1.98 (m, 2H), 3.92 (s, 2H), 4.20 (q, 2H), 4.50 (t, 1H), 6.77 (d, 2H), 7.1 (d, 2H), 7.21 (m, 4H).

**b) 4-[2-(2-(4-(4-Chlorobenzylthio)phenoxy)-1-oxobutyl)-4-methylthiazol-5-yl]butanoic acid**

The procedure described in example 10e was used with the product from 50a to give the required product as a pale yellow gum. The product was converted to the dicyclohexylamine salt which was a pale yellow solid.

Mass spectrum: m/e 504 / 506 (M+H)
M.p.: °C 114-116

$C_{37}H_{49}ClN_2O_4S_2$ requires: C 64.8 H 7.2 N 4.1 S 9.4 %, found: C 64.9 H 7.5 N 4.2 S 9.2 %

**Pharmacological Data**

*In vivo*, $PLA_2$ is responsible for the release of arachidonic acid and lysophospholipid from cell membrane phospholipids. Arachidonic acid and certain lysophospholipids are metabolised to substances which are important mediators of the inflammatory response. The usefulness of the compounds according to the invention as anti-inflammatory agents was therefore tested *in vitro* by measuring their ability to inhibit arachidonic acid release from $PLA_2$ enzyme provided with a suitable substrate.

**Cell Assay**

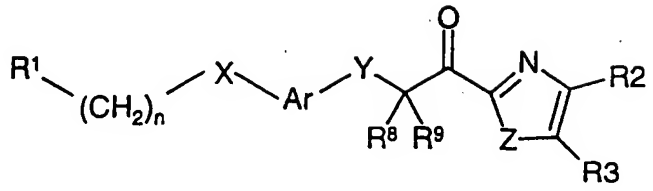
Compounds according to the invention were assayed for inhibition of release of [$^3$H]arachidonic acid from DMSO-differentiated HL60 cells in response to $Ca^{2+}$ ionophore challenge.

Cells of the human leukaemic line HL60 are differentiated to a Polymorphonuclear cell-like phenotype by treatment with 1.3% DMSO for 4 days. During the final 24 hours of differentiation, the cells are incubated with [$^3$H]arachidonic acid. After washing to remove unincorporated [$^3$H]arachidonic acid, the cells (at $2.6x10^6$/ml) are incubated for 10 minutes at 37°C with the compound of interest at concentrations up to 10μM. Arachidonic acid release is then stimulated by the addition of the $Ca^{2+}$ ionophore A23187. Control cells are incubated with vehicle alone. After 3 minutes, ice-cold MeOH is added to terminated the reaction and precipitate cellular protein and membranes. The assay reactions are then filtered to separate cellular material from the supernatant, containing the released [$^3$H]arachidonic acid. The amount of released $^3$H in the supernatant is then measured, and the inhibition of the stimulated release by the compounds is calculated.

In this screen, the compounds of the examples 1, 3, 8-10, 12, 13, 15, 16, 18, 20, 21, 24-28, 31-40, 42-44, 46 and 47-50 were tested and gave $ID_{50}$ values less than 10 μM, indicating that they had useful activity.

## CLAIMS:

1. A compound of formula I



I

wherein:-

$R^1$ represents hydrogen, C1 to 12 alkyl, phenyl or a 5 or 6 membered heterocyclic ring containing from 1 to 3 atoms selected from O, N or S, which alkyl, phenyl or heterocyclic ring is optionally substituted by halogen, or which alkyl is optionally substituted by a group J, where J is phenyl or phenyl fused with one or two benzene rings, or biphenylyl, optionally ring substituted by 1 to 3 heteroatoms selected from O, N or S, each group J being optionally substituted by C1 to 6 alkyl, hydroxy, C1 to 6 alkoxy, nitro or halogen;

for $R^2$ and $R^3$:-

(i) $R^2$ represents hydrogen, C1 to 6 alkyl or $R^{10}$-B; and
$R^3$ represents hydrogen, C1 to 6 hydroxyalkyl, C3 to 9 alkenylcarboxyl or $R^{10}$-B, wherein $R^{10}$ represents C1 to 6 alkyl and B represents COOH, $PO_3H_2$, $OPO_3H_2$, $SO_3H$, $OSO_3H$, tetrazolyl, $CONR^{11}OH$ or $CONHSO_2R^{11}$, $R^{11}$ representing hydrogen or C1 to 6 alkyl; or

(ii) $R^2$ and $R^3$ together represent a benzo ring or a six membered aromatic heterocyclic ring containing 1 to 3 nitrogen atoms, which benzo or heterocyclic ring is optionally substituted by $R^4$, wherein $R^4$ represents hydrogen, C1 to 6 alkoxy, C1 to 6 carboxyalkoxy, C3 to 9 alkenylcarboxyl, $R^{10}$-B or $-(CH_2)_pCO_2PG$,
wherein $R^{10}$ represents C1 to 6 alkyl and B represents COOH, $PO_3H_2$, $OPO_3H_2$, $SO_3H$, $OSO_3H$, tetrazolyl, $CONR^{11}OH$ or $CONHSO_2R^{11}$, $R^{11}$ representing hydrogen or C1 to 6 alkyl, and PG is allyl or *tert*-butyl and p represents zero or an integer from 1 to 6;

$R^8$ and $R^9$ independently represent hydrogen, methyl, C1 to 6 alkyl, aryl or heteroaryl, or together $R^8$ and $R^9$ represent C3 to 6 cycloalkyl or a 3, 4, 5 or 6 membered heterocyclic ring containing from 1 to 3 atoms selected from O, N or S;

Ar represents phenyl, or phenyl fused with one or two benzo rings, or biphenylyl optionally ring substituted with 1 to 3 heteroatoms selected from O, N or S, each Ar group being optionally substituted by C1 to 6 alkyl, hydroxy, C1 to 6 alkoxy, nitro or halogen;
X represents O, S, $SO_2$, $CH_2$ or SO;
Y represents O, $NR^5$ or $(CH_2)_a$, where a represents an integer from 1 to 12 and $R^5$ represents hydrogen or C1 to 6 alkyl;
Z represents O, S, CH=CH, N=N, N=CH or $NR^5$, where $R^5$ represents hydrogen or C1 to 6 alkyl; and
n represents an integer from 1 to 12;
or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

2. A compound according to claim 1 wherein $R^1$ represents phenyl, dichlorophenyl or methyl.

3. The compound according to claim 1 or 2 wherein $R^2$ is according to option (i) and represents hydrogen, methyl or $-(CH_2)_4CO_2H$.

4. The compound according to claim 1, 2 or 3 wherein $R^3$ is according to option (i), it represents hydrogen, $-(CH_2)_2OH$, $-CO_2H$, $-(CH_2)_3CO_2H$, $-(CH_2)_2CO_2H$ or CH=CH-$CO_2H$..

5. The compound according to claim 1 or 2 wherein $R^2$ and $R^3$ are according to option (ii) and $R^4$ represents $-CO_2H$, methoxy, $-(CH_2)_2CO_2H$, $-OCH_2CO_2H$ or $-(CH_2)_pCO_2PG$, where PG is allyl or *tert*-butyl and p represents zero or an integer from 1 to 6.

6. The compound according to any preceding claim wherein a represents an integer from 1 to 3.

7. The compound according to any preceding claim wherein Y represents O or $CH_2$.

8. The compound according to any preceding claim wherein X represents O or S or $SO_2$.

9. The compound according to any preceding claim wherein Z represents O, S, CHCH or $NR^5$, $R^5$ representing hydrogen or methyl.

10. The compound according to any preceding claim wherein $R^8$ represents hydrogen or methyl.

11. The compound according to any preceding claim wherein $R^9$ represents hydrogen, methyl, phenyl or isopropyl.

12. A compound of formula (I) selected from:
2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylic acid; or
1-methyl-2-[2-[4-(5-phenylpentylthio)phenoxy]-1-oxoethyl]benzimidazole; or
5-(2-hydroxyethyl)-4-methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]thiazole; or
6-methoxy-2-[2-[4-(5-phenylpentylthio)phenoxy]-1-oxoethyl]benzothiazole; or
1-methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]imidazole; or
2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]benzothiazole; or
2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]thiazole; or
2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]benzothiazole-6-carboxylic acid; or
4-methyl-2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]thiazole-5-carboxylic acid; or
4-[2-(2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid; or
2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl]thiazole; or
5-(2-hydroxyethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl]thiazole; or
5-(2-hydroxyethyl)-4-methyl-2-[2-(4-(decylsulfonyl)phenoxy)-1-oxoethyl]thiazole; or
5-(2-hydroxyethyl)-4-methyl-2-[2-(4-(benzyloxy)phenoxy)-1-oxoethyl]thiazole; or
5-(2-hydroxyethyl)-4-methyl-2-[2-(4-(benzylthio)phenoxy)-1-oxoethyl]thiazole; or
5-(2-hydroxyethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzylthio)phenoxy)-1-oxoethyl]thiazole; or
1-methyl-2-[2-(4-(5-phenylpentylsulfonyl)phenoxy)-1-oxoethyl]benzimidazole; or
2-[2-(4-(5-phenylpentylsulfonyl)phenoxy)-1-oxoethyl]benzothiazole; or
2-[2-(4-(5-phenylpentylsulfonyl)phenoxy)-1-oxoethyl]-6-methoxybenzothiazole; or
5-(2-hydroxyethyl)-4-methyl-2-[2-(4-(3,5-dichlorobenzylsulfonyl)phenoxy)-1-oxoethyl]thiazole; or
2-[2-(4-(3,4-dichlorobenzylthio)phenoxy)-1-oxoethyl]benzoxazole; or
2-[2-(4-(3,4-dichlorobenzylthio)phenoxy)-1-oxoethyl] benzimidazole; or
2-[2-(4-(3,4-dichlorobenzylthio)phenoxy)-1-oxoethyl]-6-methoxy benzoxazole; or
2-[2-(4-(3,4-dichlorobenzylthio)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylic acid; or
2-[2-(4-(3,4-dichlorobenzylthio)phenoxy)-1-oxoethyl]benzoxazole-6-carboxylic acid; or

2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl]benzoxazole-5-carboxylic acid; or
2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl]benzimidazole-5-carboxylic acid; or
3-[2-(2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl)benzoxazol-5-yl]propionic acid; or
2-[3-[4-(phenylpentyloxy)phenyl]-1-oxopropyl]benzoxazole-5- carboxylic acid; or
2-[3-(4-(5-phenylpentyloxy)phenyl)-1-oxopropyl]benzoxazole-6- carboxylic acid; or
3-[2-(2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]propionic acid; or
4-[2-(2-(4-(decylthio)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid; or
4-[2-(2-(4-(decylsulfonyl)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid; or
2-[2-(2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl)benzothiazol-6-oxy]acetic acid; or
4-[2-(2-(4-(5-phenylpentyloxy)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid; or
5-[2-(2-(4-(5-phenylpentyloxy)phenoxy)-1-oxoethyl)thiazol-4-yl]pentanoic acid; or
4-[2-(2-(4-(5-phenylpentyloxy)phenyl)-1-oxopropyl)-4-methylthiazol-5-yl]butanoic acid; or
4-[2-(2-(4-(benzylthio)phenoxy)-1-oxoethyl)-4-methylthiazol-5-yl]butanoic acid; or
2-[2-(4-(3,5-dichlorobenzyloxy)phenoxy)-1-oxoethyl]benzothiazole-6-carboxylic acid; or
4-[2-(2-(4-(5-phenylpentylthio)phenoxy)-1-oxopropyl)-4-methylthiazol-5-yl]butanoic acid; or
4-[2-(2-(4-(5-phenylpentylthio)phenoxy)-1-oxo-2-methyl-propyl)-4-methylthiazol-5-yl]butanoic acid; or
4-[2-(2-(4-(5-phenylpentylthio)phenoxy)-2-phenyl-1-oxyethyl)-4-methylthiazol-5-yl]butanoic acid; or
4-[2-(2-(4-(5-phenylpentylthio)phenoxy)-3-methyl-1-oxobutyl)-4-methylthiazol-5-yl]butanoic acid; or
2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]benzimidazole-5-carboxylic acid; or
2-[2-[4-(5-phenylpentylthio)phenoxy]-1-oxoethyl]imidazole; or
3-[2-[2-[4-(5-phenylpentylthio)phenoxy]-1-oxoethyl]-4-methylimidazol-5-yl]propenoic acid; or
2-[2-(4-(5-phenylpentylthio)phenoxy)-1-oxoethyl]pyridine; or
4-[2-(2-(4-(5-phenylpentyloxy)phenoxy)-1-oxopropyl)-4-methylthiazol-5-yl]butanoic acid; or
4-[2-(2-(4-(4-chlorobenzylthio)phenoxy)-1-oxopropyl)-4-methylthiazol-5-yl]butanoic acid; or

4-[2-(2-(4-(4-chlorobenzylthio)phenoxy)-1-oxobutyl)-4-methylthiazol-5-yl]butanoic acid; or

or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

13. The compound according to any preceding claim for use as a pharmaceutical.

14. A pharmaceutical composition including a compound according to any one of claims 1 to 12, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

15. Use of a compound according to any one of claims 1 to 12 or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, in the manufacture of a medicament, for the treatment or prophylaxis of inflammatory disease.

16. The use according to claim 15, wherein the disease is asthma.

17. A method of treating, or reducing the risk of, inflammatory disease in a patient suffering from, or at risk of, said disease, wherein the method comprises administering to the patient the compound of any one of claims 1 to 12 or a pharmaceutically acceptable salt, enantiomer or tautomer thereof.

18. The method of claim 17, wherein the disease is asthma.

19. A process for preparing the compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein the process comprises:-

(a) reacting a compound of formula IV, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, with a compound of formula V, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein formulae IV and V are as defined in claim 19 or 20; or

(b) reacting a compound of formula IV, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, with a compound of formula VI, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein formulae IV and VI are as defined in claim 19 or 20; or

(c) oxidising a compound of formula XII, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein formula XII is as defined in claim 19 or 21; or

(d) preparing a compound of formula I, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein X represents $SO_2$, by oxidising a compound of formula I, or a pharmaceutically acceptable salt, enantiomer or tautomer thereof, wherein X represents S, and optionally after (a), (b), (c) or (d) forming a pharmaceutically acceptable salt.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/02226

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 277/20, C07D 277/62, C07D 263/54, C07D 233/54, C07D 235/04, C07D 213/04 , A61K 31/426, 31/41, 31/44, A61P 29/00, 11/06
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | EP 0351194 A2 (IMPERIAL CHEMICAL INDUSTRIES PLC), 17 January 1990 (17.01.90) -- | 1-25 |
| X | WO 9603392 A1 (G.D. SEARLE & CO.), 8 February 1996 (08.02.96) -- | 1-25 |
| X | DE 2063901 A (SILBER-SCHEIDEANSTALT VORMALS ROESSLER), 20 July 1972 (20.07.72) -- | 1-25 |
| X | EP 0577003 A1 (F. HOFFMANN-LA ROCHE AG), 5 January 1994 (05.01.94) -- | 1-25 |

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 20 March 2000 | 18 -04- 2000 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Gerd Strandell/EÖ<br>Telephone No. +46 8 782 25 00 |

Form PCT/ISA/210 (second sheet) (July 1992)

# INTERNATIONAL SEARCH REPORT

| International application No. |
| --- |
| PCT/SE 99/02226 |

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| --- | --- | --- |
| X | Indian Journal of Chemistry, Volume 22B, 1983, S N Sawhney et al, "Synthesis of Some 2-Mercaptoimidazole Derivatives as Pontential Antiinflammatory Agents" page 584 - page 589<br>-- | 1-25 |
| A | EP 0735029 A1 (NIPPON ZOKI PHARMACEUTICAL CO., LTD.), 2 October 1996 (02.10.96)<br>--<br>-------- | 1-25 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/02226

**Box I** **Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17, 18
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

**Box II** **Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/02226

Claims 17-18 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

# INTERNATIONAL SEARCH REPORT

Information on patent family members

02/12/99

International application No.
PCT/SE 99/02226

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| EP 0351194 A2 | 17/01/90 | SE 0351194 T3 | |
| | | AT 107294 T | 15/07/94 |
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| | | DE 68916119 D,T | 22/09/94 |
| | | DK 346089 A | 13/01/90 |
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| | | JP 2076864 A | 16/03/90 |
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| | | US 5089513 A | 18/02/92 |
| | | US 5196422 A | 23/03/93 |
| WO 9603392 A1 | 08/02/96 | AU 3201095 A | 22/02/96 |
| | | CA 2195847 A | 08/02/96 |
| | | EP 0772606 A | 14/05/97 |
| | | JP 10504542 T | 06/05/98 |
| | | US 5668161 A | 16/09/97 |
| DE 2063901 A | 20/07/72 | NONE | |
| EP 0577003 A1 | 05/01/94 | AU 667107 B | 07/03/96 |
| | | AU 4156293 A | 06/01/94 |
| | | BR 9302737 A | 08/02/94 |
| | | CA 2099295 A | 03/01/94 |
| | | CN 1087086 A | 25/05/94 |
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| | | NO 932399 A | 03/01/94 |
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| | | ZA 9304603 A | 05/01/94 |
| EP 0735029 A1 | 02/10/96 | AT 166872 T | 15/06/98 |
| | | AU 695925 B | 27/08/98 |
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| | | JP 8325252 A | 10/12/96 |
| | | US 5900426 A | 04/05/99 |

PATENT COOPERATION TREA /

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| Applicant's or agent's file reference | **FOR FURTHER ACTION** | see Form PCT/ISA/220 as well as, where applicable, item 5 below. |
|---|---|---|
| 375458-012WO | | |
| International application No. | International filing date *(day/month/year)* | (Earliest) Priority Date *(day/month/year)* |
| PCT/US2005/031210 | 30/08/2005 | 30/08/2004 |
| Applicant | | |
| IKEN TISSUE THERAPEUTICS, INC. | | |

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [X] none of the figures is to be published with the abstract

# INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/031210

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N5/06 C12N5/08 A61L27/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61L C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
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| X,Y | US 2003/003089 A1 (AKINS ROBERT E) 2 January 2003 (2003-01-02) claims 1-4 | 1-75 |

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 31 May 2006 | 05/07/2006 |
| Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 | Authorized officer Peris Antoli, B |

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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| Y | EP 0 385 506 A (MATSUSHITA ELECTRIC INDUSTRIAL CO., LTD)<br>5 September 1990 (1990-09-05)<br>claims 1-66<br>page 11, line 11 - page 13, line 29 | 1-75 |

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PCT/US2005/031210

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